

**UNIVERSITY OF PITTSBURGH**  
**CLINICAL AND TRANSLATIONAL SCIENCE AWARD**  
**PROPOSAL**

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**ABSTRACT:**

As one of the nation's leading academic research centers, the University of Pittsburgh has both an opportunity and an obligation to take the inherent risks associated with reengineering a successful research enterprise to undertake a transformative initiative that will result in the development and advancement of clinical and translational science as a distinct discipline in western Pennsylvania. The University is committed to transforming its culture, environment, and structure to achieve this goal by forming the Clinical and Translational Science Institute (CTSI). The CTSI will serve as the integrative academic home for clinical and translational scientists across the University's six health sciences schools; Carnegie Mellon University; the University of Pittsburgh Medical Center (UPMC), one of the nation's largest and most financially successful academic health care systems; and the region. The CTSI's primary focus is to develop, nurture, and support a cadre of clinical and translational scientists by building on the University's existing clinical research training programs (Roadmap K12, K30) to establish a comprehensive program with activities ranging from early research exposure for high school students to advanced doctoral programs. Through "integration and innovation," the CTSI will excel in the development of new biomedical knowledge and the translation of that knowledge from the basic and preclinical research settings to individuals, communities, and health practice. The Children's Hospital of Pittsburgh's General Clinical Research Center (GCRC) and the four sites of the University of Pittsburgh GCRC will be reengineered, integrated, and augmented by new CTSI community-based and minority health focused centers to develop efficient, accessible, and widely used participant and clinical interaction resources. The CTSI Center for Clinical and Translational Informatics, which is developing translational research informatics tools for the NCI Cancer Biomedical Informatics Grid Initiative, will infuse informatics tools into the entire lifecycle of clinical research studies and develop an online collaborative research community. Innovative interdisciplinary research initiatives will be developed through the ten CTSI resource cores and translated to health practice via a novel CTSI community partnership program and through centralization of UPMC's extensive clinical networks. The resulting transformations in the institution, scientist, research, and health practice will improve health locally, regionally, and nationally.

## APPROACH TO MEETING THE INTENT OF THIS INITIATIVE

"*Crossing the Valley of Death*" is a descriptive term that is used in industry and by non-health related federal agencies to describe the fundamental challenge of transitioning research and development programs to operations<sup>1</sup>. The term "*Valley of Death*" is also an appropriate description for the consequences of the biomedical research enterprise's failure to effectively translate emerging laboratory discoveries to the prevention, diagnosis, and treatment of human diseases. Biomedical research must also overcome a second "*Valley of Death*" that is related to the additional barriers of translating clinical science and knowledge to clinical practice and health decision-making<sup>2</sup> (Figure). The benefits of translating basic research to clinical research and practice have been squandered to an even greater extent during the past 20 years than previously, due to the medical professions' sluggish response in translating the knowledge generated by rapid advancements in molecular genetics and cellular biology to clinically important applications.

Strategies that industry and federal agencies have adopted to "*Cross the Valley of Death*" include the development of interdisciplinary research programs, infrastructure, interfaces with user communities, observation and data access partnerships, and continuous evaluation processes<sup>1</sup>. Additional barriers that the biomedical research enterprise must overcome include<sup>3</sup>: (1) structural organization of traditional Academic *Medical Centers*; (2) academic culture impediments to collaboration; (3) shortage of "translational investigators"; (4) absence of mechanisms to facilitate translational research; (5) inadequate financial support; and (6) regulatory impediments to translation.

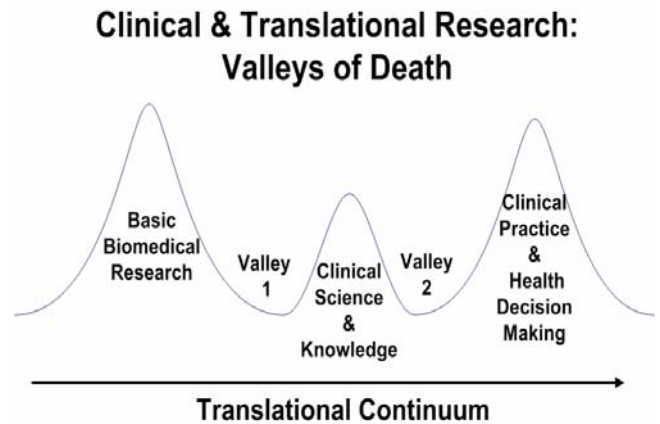
Comprehensive Academic *Health Centers* (AHCs) like the University of Pittsburgh can lead the way across the "Valley of Death" by realigning traditional administrative structures, refocusing educational programs, and tangibly rewarding team-oriented clinical and translational science—actions that, in the process, will transform the AHC's fundamental culture. As one of the nation's leading academic research centers, the University of Pittsburgh has both an *opportunity* and an *obligation* to take the inherent risks associated with reengineering a successful research enterprise to undertake a transformative initiative that will result in the development and advancement of clinical and translational science as a distinct discipline in western Pennsylvania. The University of Pittsburgh is committed to transforming its culture, environment, and structure to achieve this goal. This transformation will lead to fundamental changes in the *institution* and its training of *scientists*, its performance of *research*, and its *health practice*. **Specific goals of this transformation are:**

**1) Transformation of the *Institution***- The University of Pittsburgh will develop the Clinical and Translational Sciences Institute (CTSI) as the integrative "*academic home*" for the discipline of clinical and translational science in western Pennsylvania.

**2) Transformation of the *Scientist*** – The CTSI will transform the University's approach to the training of scientists to develop a cadre of biomedical and behavioral scientists in the new discipline of clinical and translational science.

**3) Transformation of the *Research*** – The CTSI will transform the conduct of research by 1) *integrating existing and being innovative in developing new crosscutting research methodologies and tools that will be incorporated into the development of clinical and translational research hypotheses, the promotion of translational science collaborations, the development of research educational initiatives, and the performance and regulation of clinical and translational research, and 2) facilitating the performance of highly innovative and pioneering translational research that can be rapidly developed into new disease preemption and prevention strategies, drugs, devices, diagnostics, and therapeutics and efficiently translated to humans and clinical practice.*

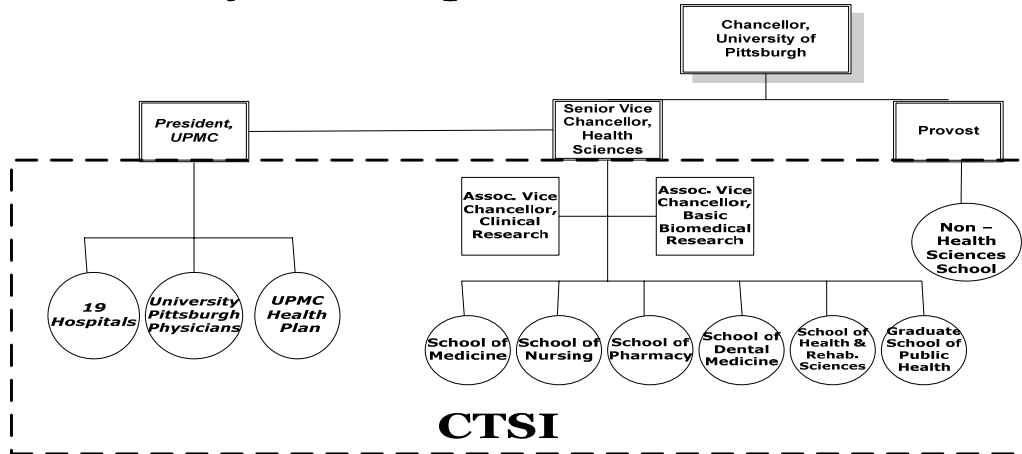
**4) Transformation of Health Practice** – The CTSI will transform regional health practice by building a "population-based laboratory" through collaborative community-based participatory programs to generate research hypotheses and develop and test new collaborative methods for translation of basic and preclinical scientific discoveries to health practice in western Pennsylvania.



## BACKGROUND

Pittsburgh is home to a uniquely robust and integrated academic **health** center (AHC) that consists of six schools of the health sciences at the University of Pittsburgh, with a remarkably close and effective collaboration with the University of Pittsburgh Medical Center (UPMC) and with other biomedically relevant schools of the University of Pittsburgh (e.g., Arts and Sciences, Education, Engineering) (Figure). The University of Pittsburgh is the only AHC in western Pennsylvania, a region with a population of 4.1 million.

### University of Pittsburgh Academic **Health** Center



The University of Pittsburgh AHC is uniquely suited to transform its academic culture to develop translational research as a discipline because of its:

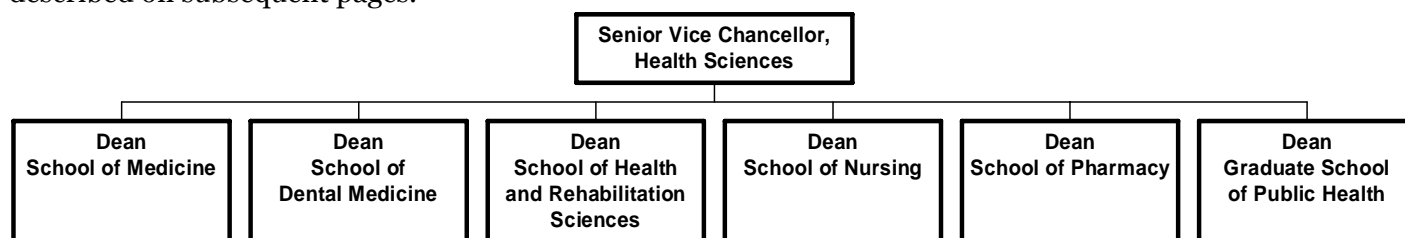
- **EXTENSIVE** history of translating innovative biomedical discoveries to humans and clinical practice (e.g., polio vaccine, liver transplantation, cardiopulmonary resuscitation)
- **INGRAINED** culture of collaboration among investigators in its six health sciences schools
- **INTEGRATION** with the rapidly evolving and successful UPMC, which today is an AHC with 19 hospitals and 350 outpatient sites in a 29-county service area (pop.=4.1 million) that accounts for 3 million outpatient visits and >165,000 inpatient admissions annually (45% county and 25% regional market share)
- **TRACK** record of institutional commitment to clinical and translational research as exemplified by its Office of Clinical Research, Health Sciences, which has transcendent responsibilities for clinical research across the six health sciences schools
- **FINANCIAL** commitment from UPMC to the research enterprise (\$177 million in FY05 as part of a 10-year affiliation agreement)
- **COMMITMENT** to clinical research education demonstrated by its institutional support for the Institute for Clinical Research Education, which serves as the home for the existing K30 Clinical Research Training Program (CRTP), Roadmap K12 Multidisciplinary Clinical Research Scholars Program (CRSP), and School of Medicine-supported Clinical Scientist Training Program (CSTP).
- **HISTORY** of establishing interdisciplinary categorical translational institutes in partnership with UPMC and charitable foundations (e.g., University of Pittsburgh Cancer Institute, McGowan Institute for Regenerative Medicine, Institute on Aging, Drug Discovery Institute)
- **NOVEL** relationships with industry partners (e.g., IBM, Intel) and Carnegie Mellon University (CMU) to co-develop, translate, and commercialize emerging technologies that improve disease prevention, diagnosis, and treatment
- **ESTABLISHED** partnership with RAND (RAND-University of Pittsburgh Health Institute) to empirically test and evaluate in the western Pennsylvania region the most promising health interventions; identify potential clinical, organizational, and systemic barriers to the implementation of these interventions; devise and implement strategies to overcome such barriers; and demonstrate how to sustain the interventions in day-to-day community practice regionally and nationally

The CTSI will have the transformational mission of strategically melding the AHC's existing clinical and translational research and training components to form a new, more formal "academic home" for the **discipline** of clinical and translational science in western Pennsylvania. Among these existing components are:

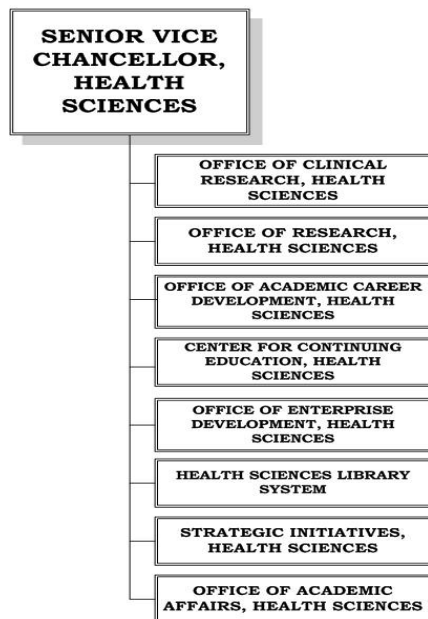
(1) **University of Pittsburgh-** The University of Pittsburgh and its six health sciences schools (Dental Medicine, Health and Rehabilitation Sciences, Medicine, Nursing, Pharmacy, Public Health) comprise one of

the nation's leading academic centers for biomedical research. Pitt scientists are engaged in funded studies on topics ranging from the most basic investigations in fields like DNA repair and structural biology to the more translational drug discovery and cancer immunology to the population-based epidemiology of chronic disease to the very applied assistive device development and investigations aimed at increasing patients' adherence to treatment and enrolling community members in clinical trials. Faculty serve as principal investigators on ~1,000 research grants, 148 first (K) awards, >60 program project grants, and 51 training grants funded by NIH. **In FY 2004, the University of Pittsburgh ranked 7<sup>th</sup> among educational institutions and affiliates in NIH funding (\$396 million).** The School of Medicine ranks eighth, Nursing ranks seventh, Health and Rehabilitation Sciences ranks 10th, the Graduate School of Public Health ranks third, Pharmacy 11th and Dental Medicine 28<sup>th</sup>. The following School of Medicine departments ranked among the top 10 in NIH funding in FY04: Anesthesiology (4); Emergency Medicine (3); Molecular Genetics and Biochemistry (5); Neurobiology (6); Neurological Surgery (2); Obstetrics, Gynecology, and Reproductive Sciences (2); Orthopaedic Surgery (9); Otolaryngology (6); Pathology (5); Pediatrics (7); Pharmacology (8); Physical Medicine and Rehabilitation (9); Psychiatry (1); Radiology (8); Surgery (4); and Urology (7).

Administratively, the six health sciences schools individually and collectively report to the Senior Vice Chancellor for the Health Sciences (SVCHS), Arthur S. Levine, M.D. (Figure). The health sciences schools are described on subsequent pages.



This unifying organizational structure facilitates interdisciplinary collaborations in research, education, administration, and clinical care among 2500 faculty across the range of health sciences disciplines. The SVCHS has established several offices with transcendent responsibilities across the health sciences schools that provide a unique opportunity to readily transform the clinical and translational research enterprise under the direction of the CTSI. The following offices will play integral roles in the CTSI:



**a) Office of Clinical Research, Health Sciences (OCR)** -Under the leadership of the Associate Vice Chancellor for Clinical Research, Health Sciences, and CTSI Principal Investigator, Steven E. Reis, M.D., OCR serves as the institutional hub for clinical research and the advocate for clinical researchers. OCR facilitates the process and promotes the value of clinical research at the AHC and serves as a focal point for the *innovative* development of new institutional resources and *integration* of existing resources that support clinical research. OCR's broad institutional authority gives it both the capability and the mandate to guide the transformative process in clinical and translational science activities under the auspices of the CTSI. As the senior administrator for clinical research, Dr. Reis plays an integral role in institutional policymaking vis-à-vis the clinical and translational research enterprise. His experience as an established clinician scientist who maintains an active clinical and translational research program that focuses on the pathophysiology of race and gender differences in cardiovascular disease provides him with an overview of the ever-changing needs of and barriers to clinical and translational research that must be addressed by institutional resources and policies, as well as with insight regarding the need to address these barriers effectively,

efficiently, and in an expedited manner through the development of institutional programs. Dr. Reis has been designated by the University as the CTSI PI and founding Director and OCR has been designated to serve as the CTSI administrative home.

**b) Office of Research, Health Sciences (OORHS)**– OORHS fosters the basic biomedical research enterprise within and across the six schools of the health sciences. OORHS develops basic research resources and core facilities; administers the UPMC-supported Competitive Medical Research Fund (CMRF); coordinates research space and infrastructure assignment, renovation, and construction; facilitates multi-investigator and multidisciplinary grant application preparation; develops and administers resources for grant application

development; provides guidance to new research faculty; and oversees the Division of Laboratory Animal Resources. These roles will provide the CTSI with an institutional mechanism to develop translational core facilities, administer its Pilot and Collaborative Studies and Novel Clinical and Translational Methodologies programs, and plan and build its physical “home” as outlined in the CTSI space plan.

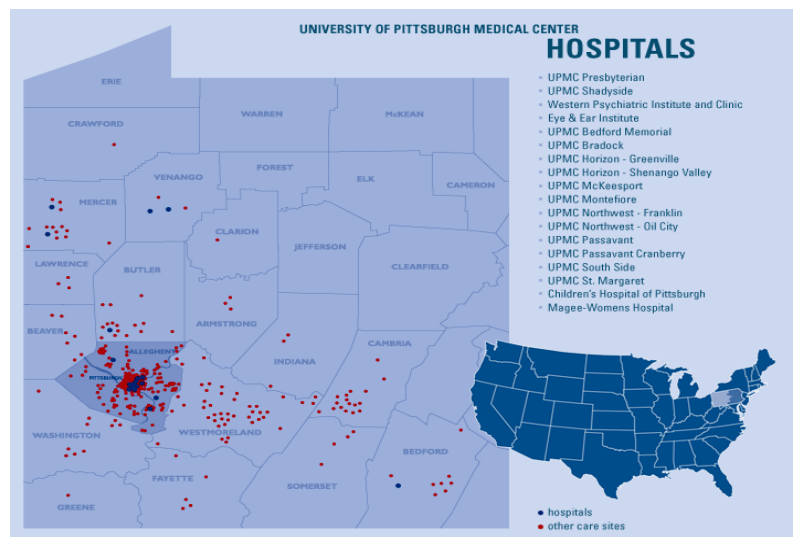
**c) Office of Academic Career Development, Health Sciences (OACD)** - OACD provides the core mentoring curriculum for the University’s K12 CRSP, K30 CRTP, and CSTP training programs. As part of the CTSI, OACD , will 1) foster a supportive environment and provide programs that promote successful academic career development for clinical and translational scientists, 2) facilitate the adoption of best mentoring practices, 3) support the recruitment, retention, and advancement of populations facing special challenges in academic careers (e.g., women, under-represented minorities), and 4) serve as a national resource and model of comprehensive academic career development in the discipline of clinical and translational science.

**d) Center for Continuing Education in the Health Sciences (CCEHS)** - In the CTSI, CCEHS will serve as a resource to promote interdisciplinary evidence-based practice education by 1) coordinating continuing education initiatives that are designed to develop "research informed" health professionals; 2) developing the CTSI Community Outreach Speakers Bureau to build a “research-informed” lay community, 3) organizing the annual CTSI “Synergies in Health Sciences Research Day,” 4) educating and certifying health professionals and staff who conduct research, and 5) reconfiguring its existing Rapid Deployment Continuing Education program to facilitate the translation of high impact clinical and translational research findings to clinical practice.

**e) Office of Enterprise Development, Health Sciences (OED)** - OED programs that catalyze academic-industry collaborations will serve as a framework for the CTSI Catalytic Program.

**f) Office of Academic Affairs, Health Sciences (OAA)**- OAA is responsible for institution-wide educational programs that target interdisciplinary health sciences researchers. Ongoing programs that will serve as models for CTSI activities include: the SVCHS Laureate Lecture Series; the SVCHS Research Seminar Series (focuses on exceptional interdisciplinary research being conducted by junior investigators); the annual "Science" Celebration (broad-based showcase of University science and technology that is open to the regional science and technology enterprise and the public); and the Mini-Medical School (bi-weekly presentations to the general community on health care topics and research). This latter program will be expanded as part of the CTSI’s initiative to develop a “research informed” lay community.

**(2) University of Pittsburgh Medical Center (UPMC)** – The unifying administrative structure of the six health sciences schools serves as a foundation for the University's very close and integrative affiliation with UPMC, one of the nation’s largest and most financially successful academic health care systems. This affiliation provides the health sciences schools with opportunities to offer programs in biomedical research, education, and clinical training in virtually every medical specialty. Although they have evolved over the last decade to be legally separate and distinct entities, the University and UPMC are interdependent and philosophically aligned in support of their common commitment to excellence in research, education, and clinical care. As a provider of state-of-the-art medical services through its comprehensive network of 19 community, secondary, and tertiary care hospitals (Figure); specialty hospitals (Children’s Hospital of Pittsburgh, Magee-Womens Hospital, Eye and Ear Institute, Western Psychiatric Institute and Clinic); cancer centers (UPMC Cancer Centers, with the Hillman Cancer Center as the hub and 41 community-based centers throughout the region), 350 specialized outpatient facilities; rehabilitation centers; and a provider of health insurance products through the UPMC Health Plan, UPMC is renowned for translating new scientific findings into innovative clinical care and for supporting the development of new medical technology. Together, the University of Pittsburgh and UPMC have raised the standard of medical excellence in western Pennsylvania and positioned health care as a driving force in regional economic development.



UPMC's attributes include the following:

### **Organizational Profile**

- 19 hospitals with >4,000 licensed beds.
- >4,000 affiliated physicians (~2,100 employed) across all specialties; faculty practice of 1,350.
- >350 physician offices and other specialized outpatient centers.
- 1,300 medical residents in 82 specialty areas; 1,200 nurses in training.
- Rehab network: >50 hospital and outpatient facilities for physical, occupational, and speech therapies.
- 14 retirement and long-term care independent living, assisted living, and skilled nursing facilities.
- >40,000 employees.
- >\$5 billion annual budget; Aa3 rating by Moody's Investors Service.
- Contributes >\$200 million annually in community service, charity, and uncompensated care.
- UPMC's Center for Biosecurity is networking all health-care providers within the region.

### **Annual Patient Activity**

- >165,000 inpatient admissions; >3 million outpatient visits; >350,000 emergency visits; >115,000 surgeries; > one million home care visits.

### **Market Profile**

- Primary market area includes the 29 counties of western Pennsylvania (population=4.1 million) including urban, suburban, and rural communities; significant elderly population; diverse socioeconomic representation.
- **45% market share of Allegheny County; 25% share of western Pennsylvania.**

### **Support for Research**

- Has designed clinical models that facilitate the translation of research findings into clinical settings (e.g., Institute for Rehabilitation and Research).
- Invested \$150 million for the construction of the Hillman Cancer Center, a 300,000 sq. ft. integrated cancer research and outpatient clinical care facility, and an adjacent 100,000 sq. ft. UPMC Cancer Pavilion. Has committed to construct a second 350,000 sq. ft. research facility.
- Constructing a 230,000 sq. ft. facility for pediatric research.
- Constructing a dedicated research facility for women and infant health research.
- Contributed \$10 million toward the construction of the recently opened Biomedical Science Tower Three, a 330,000 sq. ft. research building that houses state-of-the-art research core facilities and multi- and interdisciplinary research programs.

UPMC has designated UPMC Braddock Hospital as its flagship hospital for taking a leadership role in working with CTSI to eliminate health disparities within the region. This hospital was chosen for its tradition of service to low income, minority communities located within its service area southeast of Pittsburgh, several of which are economically distressed. Surrounding communities are 70% African-American; 35% of the population is below the poverty line, with 54% of children <18 years old living in poverty. Median family income is \$20,669; the unemployment rate is nearly 16%. UPMC Braddock has a proven track record of providing nontraditional hospital services within the community, including implementation of a new model of health care delivery in partnership with clinical and community organizations to fulfill the Healthy People 2010 goals. Braddock Hospital will serve as the site for the innovative CTSI *Braddock Minority Health Clinical and Translational Research Center (CTRRC)*. This CTRRC will improve health and reduce racial disparities by providing on-site performance of higher and lower-intensity research studies.

## **INNOVATION/METHODS TO ACHIEVE GOALS**

**GOAL 1- Transformation of the Institution- The University of Pittsburgh will develop the Clinical and Translational Sciences Institute (CTSI) as the integrative "academic home" for the discipline of clinical and translational science in western Pennsylvania.**

**Overview of Transformation of the Institution:** The CTSI will transform the institution by becoming the academic home and institutional advocate for clinical and translational science. This transformation will occur through an unprecedented collaborative effort among the **University's six health sciences schools; the University of Pittsburgh Medical Center; RAND; Carnegie Mellon University; and local health professionals, foundations, lay communities, and industry.** The CTSI's primary focus is to build on the University's extensive record of clinical and translational research training, including its K30 and Roadmap K12 programs, to develop, nurture, and support a cadre of highly trained clinical and translational



scientists. The CTSI's long-term goal is to improve health in western Pennsylvania through the conduct of clinical and translational research. Through "*integration and innovation*," the CTSI will excel in the development of new biomedical knowledge and the translation of that knowledge from the basic and preclinical research settings to individuals, communities, and clinical practice. This goal will be accomplished by transforming the University's extensive activities in basic, translational, and clinical research through novel institutional *integration* of existing programs and the development of *innovative* interdisciplinary research initiatives. The resulting transformation will improve health locally, regionally, and nationally.

**Key Functions Conducted To Achieve Goal 1: Transformation of the Institution:** The transcendent responsibility of the SVCHS for the six schools of the health sciences provides him with the authority to transform the institution by establishing the CTSI as an independent interdisciplinary health sciences institute with overarching administrative authority, educational responsibilities, and resources across these schools. By selecting the Associate Vice Chancellor for Clinical Research, Health Sciences, as the CTSI PI and Founding Director, the SVCHS has made the commitment that the CTSI will be a distinct entity external to any individual school, department, division, center, or program. This framework guarantees the development of clinical and translational science as a discipline within the AHC, which would not be possible if the CTSI had traditional departmental status within a single school such as the School of Medicine.

**Faculty, Staffing, and Direction of the CTSI:** The CTSI will serve as the regional academic home for clinical and translational science to provide 1) advanced degree training and career development for a cadre of interdisciplinary clinical and translational scientists; 2) a focus for interactions and collaborations among investigators with common interdisciplinary translational research interests, 3) a conduit for the exchange of state-of-the-art basic and clinical information and ideas that form the foundation for emerging clinical and translational research; and 4) infrastructure, resources, and pilot funding to members to encourage and support the development and implementation of interdisciplinary clinical and translational research throughout the academic, clinical, and general communities of western Pennsylvania. CTSI members will be predoctoral students, postdoctoral trainees, and faculty members at all levels from the six health sciences schools, from several non-health science schools, and from the adjacent Carnegie Mellon University (CMU), which brings its excellence in a variety of biomedically relevant disciplines and its well established track record of collaborations with the University of Pittsburgh related to basic and translational research. CTSI membership criteria, responsibilities, and benefits that are designed to promote substantial member commitment to the CTSI are described in **Table 1**. The University of Pittsburgh has strongly indicated its understanding of the institutional importance of clinical and translational science as a discipline, and the need for an integrative administrative structure, by its formation of the CTSI and by providing the CTSI with authority to confer secondary appointments in conjunction with "traditional" primary academic appointments (e.g., "assistant professor of pediatrics and clinical and translational science"). This new policy provides the CTSI with an academic visibility that exceeds that of all other interdepartmental entities (e.g., institutes, centers) in the schools of the health sciences.

The University has made an even more important commitment to the development of clinical and translational science as a discipline by allowing the CTSI to play an integral role in the promotions and tenure processes for its members. Under the direction of the SVCHS, the six schools of the health sciences will amend their bylaws in accordance with University policy to ensure that the CTSI is fully integrated into the promotions and tenure processes for CTSI members. The CTSI Steering Committee (see "Governance") will have institutional authority to 1) nominate a CTSI member for promotion and/or tenure in her/his primary department, 2) provide *ad hoc* members to departmental promotions committees, 3) identify references from local and national clinical and translational science communities, and 4) formally submit letters supporting promotions and/or tenure. The promotions and tenure processes in each health sciences school will be modified to incorporate criteria including: contributions to interdisciplinary clinical and translational science and education, multidisciplinary research collaborations, and mentoring of CTSI Scholars.

The CTSI's designated stature as a centrally important and transdisciplinary academic organization is based on an administrative framework that has been previously developed and successfully employed at the AHC for two other large interdisciplinary programs. As an example, the *University of Pittsburgh Cancer Institute (UPCI)* is the central focus for all cancer research at the University of Pittsburgh, UPMC, and CMU and has been designated by NCI as a Comprehensive Cancer Center since 1989. UPCI is directed by Ronald B. Herberman, MD, who also serves as the Associate Vice Chancellor for Cancer Research. UPCI has 11 CCSG funded cancer programs in basic, clinical, translational, and population sciences research and an additional 16 disease-site and developing programs designed to foster multidisciplinary cancer research. UPCI members have primary appointments in traditional academic departments in any of the schools at the University or CMU and perform

cancer-relevant research. In 2002, after three years of planning and support from the SVCHS and UPMC, UPCI moved to a newly constructed cancer-dedicated facility with 178,000 sq. ft. of research facilities, 185,000 sq. ft. of outpatient facilities, and 100,000 sq. ft. of office space. In 2005, UPCI's total funding reached ~\$159 million.

CTSI faculty and staff will be drawn from throughout the schools of the University and CMU, including:

**1. School of Medicine (SOM)** - The SOM has ~1,300 faculty members and 26 departments. Clinical and several basic science departments have portfolios of clinical and translational research related to the relevant discipline, although the school's well established collaborative culture has led to a focus on the performance of clinical research by interdisciplinary groups of investigators from multiple SOM departments and from multiple schools. Broad thematic areas of emphasis include:

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• Molecular Biology</li> <li>• Structural Biology</li> <li>• Cell Biology</li> <li>• Developmental Biology</li> <li>• Immunology</li> <li>• Computational Biology</li> <li>• Neurobiology</li> <li>• Reproductive Biology</li> <li>• Drug Discovery and Design</li> <li>• Organ transplantation</li> <li>• Tissue Engineering/Stem Cell</li> <li>• Artificial Organ and Medical Device Development</li> <li>• Robotics</li> <li>• Women's Health</li> <li>• Health and Health Care Disparities</li> </ul> | <ul style="list-style-type: none"> <li>• Pediatrics</li> <li>• Clinical Trials/Clinical Epidemiology</li> <li>• Cancer Diagnosis and Therapy</li> <li>• Cardiovascular disease</li> <li>• Gene Therapy</li> <li>• DNA repair</li> <li>• Nanoscience</li> <li>• Health Services Research</li> <li>• Vaccines</li> <li>• Medical Informatics</li> <li>• Behavioral Health/Psychiatry/Neuroscience</li> <li>• Neurological Surgery</li> <li>• Aging/Geriatrics</li> <li>• Chronic Disease Prevention</li> <li>• Genetics (pathology, diagnosis, cancer, behavior, environment, pharmaco-)</li> </ul> |
|--|---|

Representative medical school departments are described below:

- *Department of Pediatrics*- The Department of Pediatrics has 207 full-time faculty in 20 subspecialty divisions involved in combinations of clinical, educational, and research activities. There are >300 community practitioners on the clinical faculty, most of whom are linked via the Children's Community Pediatrics network. The Department runs three residency programs: categorical pediatrics (72 positions), medicine-pediatrics (16), and pediatrics-psychiatry-child psychiatry (5). The Department also runs ACGME-accredited fellowship training programs in 16 subspecialties. Each program requires 21-24 months of research training. The research program had an NIH funding base of \$20.5 million in FY05 (compared to \$7 million in FY00). The Department constitutes 90% of the Children's Hospital of Pittsburgh (CHP) faculty. CHP is the only referral center in the tri-state area devoted to pediatrics. CHP's 230-bed tertiary care facility treats patients from birth through age 18 and provides most of the pediatric inpatient care within a 50-mile radius and virtually all of the tertiary care within a 100-mile radius. CHP physicians annually admit >15,000 patients and conduct >200,000 outpatient visits. As a result of its merger with UPMC in 2000, the CHP/UPMC partnership committed \$575 million to build a new 1.1 million sq.ft. 300-bed pediatric hospital and ambulatory care center and a 230,000 sq.ft. pediatric research building (Figure, completion date 2008). Construction includes dedicated space for the CTSI Pediatric Clinical and Translational Research Center (3500 sq. ft.). Additional space for CTSI pediatric research network administration will be provided, as well as state-of-the-art animal facilities and imaging, genetic engineering, physiology, and behavioral cores that will occupy one of the eight 29,000 sq. ft. floors in the new research building. The CHP/UPMC merger has also realized a commitment of \$200 million for translational pediatric research over the next 10 years. After construction of the new CHP, the current facility will undergo a complete renovation; plans include 100,000 sq.ft. of space dedicated to the CTSI



to serve as the AHC home for clinical and translational science. This dedicated space forms the framework for Phase 2 of the CTSI space plan.

- **Department of Obstetrics, Gynecology, and Reproductive Sciences**- The Department of Obstetrics, Gynecology, and Reproductive Sciences is located at Magee-Womens Hospital of UPMC (MWH). MWH is the largest private women's hospital in the United States and is the tertiary referral center for obstetrics and gynecology in the tri-state area. It is the region's major clinical resource for high-risk obstetrics, neonatology, newborn screening, breast cancer, gynecological oncology, urogynecology, assisted reproductive technology, complex menopause, infectious diseases, and genetics. MWH is a full-service women's hospital with 266 beds and a satellite network of 17 Womancare Centers. Each year, there are >200,000 outpatient visits at MWH and its Womancare Centers. In affiliation with MWH, the Magee-Womens Research Institute (MWRI) became the first research center in the United States to focus exclusively on the health issues of women and infants. It remains the only such facility affiliated with a major university teaching and research hospital. MWRI's interactive approach to research, affiliation with UPMC, and location adjacent to MWH uniquely positions MWRI as a center for translational research involving a broad range of women's and infants' health problems. MWRI will oversee the CTSI *Magee Womens Hospital CTRC* at MWH, which will serve as the center for primary-care based women's specialty clinical and translational research in the AHC.

- **Department of Psychiatry**- The Department of Psychiatry at Western Psychiatric Institute and Clinic (WPIC) is a national leader in clinical and translational research, guided by multidisciplinary collaboration and multiple responsibilities shared among treatment and research teams. The 185 faculty place a special emphasis on ensuring that the research environment provides bridges to clinical treatment by focusing on the etiology of mental disorders; clinical treatment trials; methodological issues; and evaluation of outcomes. The Department has 180 funded projects (\$76 million) and has been ranked #1 in NIH funding for Departments of Psychiatry since the mid-1980's. The Department has several large training programs, including seven T32 grants and also has more than 40 active career development awards, including 20 KO1s and 19 K23s. The Department houses five federally funded centers of excellence. WPIC will serve as the home for the CTSI *Neuroscience CTRC*, which will serve as an institutional resource for the investigation of the interactions among chronobiology, sleep, and a range of clinical conditions.

- **Department of Biomedical Informatics** - The transformation that the CTSI will catalyze will be facilitated by ongoing major organizational changes in the SOM, including the formation of the new Department of Biomedical Informatics. CTSI planning played an integral role in the University's decision to form this department, which resulted from the merging of the Centers of Biomedical Informatics and Pathology and Oncology Informatics. The creation of this department and the integration of the GCRC and its informatics tools into the CTSI provide the CTSI with a strong translational informatics foundation from which to begin the transformative efforts that will provide a central informatics resource to CTSI members and the national CTSA Consortium. This department has strong institutional commitment from the SOM (\$1.9M in addition to ongoing support for the merged entities the department comprises) and UPMC (\$5M) as well as the space (~75,000 sq. ft.) needed to promote the integration proposed in this application.

**2. Graduate School of Public Health (GSPH)** – GSPH's academic activities include doctoral and translational research programs in the Departments of Behavioral and Community Health Sciences, Biostatistics, Environmental and Occupational Health, Epidemiology, Health Policy and Management, Human Genetics, and Infectious Diseases and Microbiology; the multidisciplinary MPH program for doctoral level public health professionals; and certificate programs. The school has developed 14 specialized research centers including the Center for Minority Health; the Center for Rural Health Practice; the Epidemiology Data Center; and the Health Policy Institute. GSPH has 142 full-time faculty, and, in FY 05, had \$76 million in research funding with 61 NIH funded grants (\$45.3 million), ranking GSPH third in NIH support among the nation's public health schools. The recently appointed GSPH dean, Donald Burke, MD, will also serve as the first Associate Vice Chancellor for Global Health, Health Sciences, and Director of the interdisciplinary Center for Vaccine Research. In these positions, he will take an active leadership role in developing broad interdisciplinary translational research initiatives that will be supported, in part, by the CTSI.

**3. School of Dental Medicine (SODM)** – The SODM has 88 full-time, 81 part-time, 83 adjunct, and 20 emeritus faculty and offers a four-year doctor of dental medicine degree. The school offers postdoctoral residency certificates in eight specialties (including pediatric dentistry) and degree programs in dental hygiene. The school has integrated evidence-based dentistry into the pre-doctoral curriculum to foster critical review

and clinical application of the scientific literature. This philosophy serves as a model for the CTSI evidence-based practice education initiative that will develop “research informed” health professionals. SODM is in the process of integrating its preclinical courses into a joint curriculum with the SOM. SODM has 59 externally funded research grants in fields including dental informatics; genetics; public health; behavioral sciences; and tissue engineering. Major research centers include the Center for Craniofacial and Dental Genetics; the Center for Oral Health Research in Appalachia; and the Center for Craniofacial Regeneration. The required student research program is supported, in part, by an NIDCR T32 training grant and an internally-supported Summer Research Scholarship Program. The school’s nationally prominent Center for Dental Informatics will play a key role in the CTSI Center for Clinical and Translational Informatics.

**4. School of Nursing (SON)** -The SON has nearly 1,000 students at the undergraduate, master’s, and doctoral levels. The graduate programs, which are ranked 10<sup>th</sup> in the nation, have recently transitioned to an evidence based practice (EBP) model that will serve as a foundation for the CTSI Community PARTners Program EBP programs for health practitioners. The undergraduate programs train entry level nurses, with most graduates assuming positions in acute care institutions throughout the region. Graduates from the master’s and professional doctoral programs are involved in patient management, application of research to practice, the development of practice protocols and procedures, and the education of professionals. They are also involved in research as clinical coordinators, patient educators or interventionists, or technical assistants. The PhD program is designed to produce clinical scholars. The school’s research program ranks 7<sup>th</sup> in NIH research funding. Major research foci include: (1) chronic disorders, emphasizing self-management and behavioral interventions; (2) critical care, emphasizing nursing management of the critical care patient; (3) informatics, emphasizing consumer informatics; and (4) genetics, addressing genetic factors underlying nursing management of patients. The SON has extensive informal clinical networks that are used to recruit subjects and to conduct research protocols. These include the physician practices and hospitals within and external to UPMC, home health care services, assisted living facilities, public school nurses, selected local pharmacies, the county health department, and 33,000 local alumni.

**5. School of Pharmacy (SOP)** -The SOP is home to 400 PharmD professional students, 30 graduate students, 14 post-PharmD residents and fellows, and postdoctoral trainees. SOP research spans a broad range from patient outcomes and human clinical research to molecular genetics. SOP has five programmatic research centers: the Center for Pharmacogenetics; the Center for Education and Drug Abuse Research (CEDAR); the Pharmacodynamic Research Center; the Neuroendocrinology Research Group; and the Center for Pharmacoinformatics and Outcomes Research (CPOR). The SOP ranks 11<sup>th</sup> among schools of pharmacy based on NIH funding. The SOP was one of the nation’s first to develop a clinical scientist (PhD) program that trains pharmacy students to become independent clinical researchers. The School partners with the Rite Aid Corporation in a community-based pharmacy initiative to provide a medication therapy management service model, training program, and software to support acquisition of patient data and communication of results to patients and their physicians. SOP is expanding these services to develop a community pharmacy research network that will include research data collection and management, implementation of the CTSI patient registry, recruitment of research subjects, and evidence-based practice training for community pharmacists.

**6. School of Health and Rehabilitation Sciences (SHRS)** – SHRS conducts undergraduate, graduate, and doctoral programs in Communication Science and Disorders; Health Information Management; Occupational Therapy; Physical Therapy; Rehabilitation Science and Technology; and Sports Medicine and Nutrition. Interdisciplinary collaboration is pervasive across departments. Faculty receive \$8-\$10 million annually in clinical and translational research awards from NIH, NSF, VA, NIDRR, Navy, Army, DOD, NTIA, Commerce, PA, and foundations. SHRS has two NIDRR Rehabilitation Engineering Research Centers and important interdisciplinary collaborations with investigators throughout the AHC; the School of Engineering; and CMU. SHRS is developing a major effort in computational modeling for clinical research, with an emphasis on merging regenerative medicine and rehabilitation to create a new research paradigm for “regenerative rehabilitation.” SHRS is also engaged with Medical Robotics at CMU to establish a new area of study and enterprise in quality of life technology for self-determination for older adults and people with disabilities. SHRS has extensive clinical networks and community outreach programs in collaboration with UPMC.

The institutional transformation that will occur as a direct result of CTSI’s founding will change the culture of the AHC’s scientific community, as described throughout this application. To accomplish this transformation, the CTSI will develop **10 key functions** (“Cores”), which are described in sections of this application.

**GOAL 2 – Transformation of the *Scientist* – The CTSI will transform the University’s approach to the training of scientists to develop a cadre of biomedical and behavioral scientists in the**

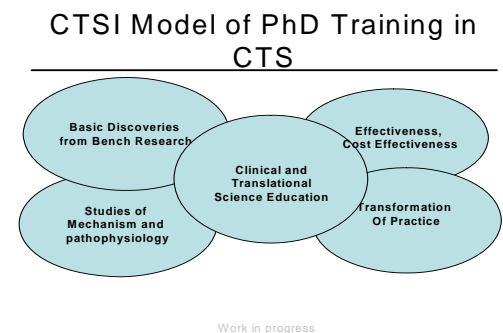
## **new discipline of clinical and translational science.**

**Overview of Transformation of the *Scientist*:** The University of Pittsburgh was awarded one of the original seven NIH Roadmap Initiative K12 grants, the Multidisciplinary Clinical Research Scholars Program (CRSP), in 2004. While developing the CRSP proposal and implementing the program, a diverse group of multidisciplinary faculty become ardent advocates of the critical importance of interdisciplinary research and the crucial need for revamping research training to encourage multidisciplinary team building, team mentoring, and collaboration. The institution's experience in implementing the CRSP, as well as the K30 Clinical Research Training Program (CRTP) and the SVCHS-supported Clinical Scientist Training Program (CSTP) for medical students, has provided insight into the needs for, and complexity of, multidisciplinary research training programs that target a broad range of trainees in all disciplines across the health sciences.

The CTSI will transform the “clinical and translational scientist” by developing a comprehensive program designed to educate and train individuals from pre-college to graduate and professional levels in the discipline of clinical and translational science. This goal will be accomplished by (1) building on an established record of formal clinical research training to train students at all educational levels; (2) expanding educational opportunities to provide multidisciplinary researchers with opportunities to obtain advanced master's and doctoral degrees in clinical and translational science; and (3) enhancing the academic career development of clinical and translational scientists through an institutional commitment to provide integrated educational, mentoring, and funding resources. The CTSI Research Education, Training, and Career Development Program will train a cadre of clinical and translational scientists who will approach science with a philosophy that is fundamentally different from that of traditional basic and clinical scientists. This philosophy is based on the concept of “interdisciplinarity” and team-oriented approaches to the conduct of research. The resulting product will be clinical and translational scientists who perform interdisciplinary research that focuses on disease “preemption,” the effects of multiple biological pathways and disease processes, “holistic” approaches that address the entire lifecycle of diseases processes, and the use of large clinical data repositories to generate and test innovative hypotheses.

## **Key Functions Conducted To Achieve Goal 2: Transformation of the Scientist**

**a) CTSI Research Education, Training, and Career Development Program-** The CTSI Research Education, Training, and Career Development Program will train a cadre of clinical and translational scientists. To transform the “scientist” and to develop education, training, and career development activities focusing on clinical and translational research, the CTSI will: 1) develop a new conceptual framework for a clinical and translational scientist (Figure); 2) integrate the existing K12 Multidisciplinary CRSP, K30 CRTP, and SVCHS-supported CSTP into the CTSI ; 3) develop an innovative CTSI T32 Program with a common core of training elements for all pre-doctoral trainees in the six health sciences schools, short-term practical research experiences in a laboratory or research program for selected pre-doctoral trainees, a certificate program in clinical and translational research, and a PhD program; 4) implement a faculty development program in clinical and translational research to encourage research faculty to broaden their perspectives with respect to the discipline of clinical and translational science; 5) develop a certification program in the conduct of research for research staff; 6) develop a career development program for all research career (K) awardees and trainee (T) grantees in the health sciences schools; 7) develop a program for residents and postdoctoral fellows to jumpstart their research careers in clinical and translational research; 8) design programs for pre-college and undergraduate students that provide early exposure to clinical and translational research based on the philosophy that such exposure will increase the pool of researchers in this area; and 9) develop informational programs about clinical and translational research and participation in research for health professionals and the public.



**b) Pilot and Collaborative Translational and Clinical Studies-** Advanced training is a major factor in the development of successful clinical and translational scientists. CTSI members will generate novel translational research hypotheses and will have access to state-of-the-art translational research tools to rapidly and efficiently implement their studies (see Goal 3). However, the study of novel hypotheses by CTSI Scholars will also require pilot funding to generate preliminary data that are critical to supporting grant applications.

The CTSI Pilot and Collaborative Translational and Clinical Studies Core will provide grant funding opportunities for CTSI Scholars by *integrating* existing AHC pilot research grant programs and *innovatively developing* new collaborative interdisciplinary grant opportunities. For example, CTSI will actively promote the UPMC-endowed Competitive Medical Research Fund (CMRF), which provides research support through competitive grants to scientists across the biomedical sciences. Two of the three CMRF funding categories support junior CTSI Scholars: “New Investigator” and “Collaborative Research” awards. The CTSI will not only enhance this funding mechanism but will 1) develop additional thematic grant programs that are linked to multidisciplinary research educational programs, 2) provide enhanced access to other existing programmatic funding mechanisms (e.g., UPCI Head and Neck Cancer SPORE, Center for Minority Health EXPORT program), 3) develop a “virtual venue” to facilitate collaborations between junior and senior investigators across health science disciplines, and 4) pilot a Clinical Investigation Team Building (CITB) Program to guide junior faculty members through the entire process of building a clinical or translational research team and of designing and implementing a clinical study. These opportunities will support the career development of CTSI Scholars.

**c) Design, Biostatistics, and Clinical Research Ethics-** To transform the “scientist,” it is critical to provide formal guidance on the direct application of knowledge acquired in the CTSI Research Education, Training, and Career Development Program to the practice of research. This guidance must be counterbalanced by a need to avoid having Scholars focus excessive time and effort on specific components of the research process (e.g., statistical analyses). The CTSI Design, Biostatistics, and Clinical Research Ethics Core (DBE) will provide centralized services to CTSI Scholars, Associate Members, and Members. The DBE will offer technical assistance throughout the entire research process from idea generation through study design, analysis, and dissemination. This core will provide expert consultations on, and training in, research methodology; measurement adaptation and evaluation; form design; data management and analysis.

**d) Community PARTners (*Partnering to Assist Research and Translation*) Program-** To facilitate the translation of biomedical discoveries to individuals and communities and to promote the generation of research hypotheses that are relevant to local populations, it is critical for scientists to understand the principles of community-based participatory research<sup>4</sup> (CBPR). A major goal of the CTSI Community PARTners Program is to develop a cadre of “community-informed” scientists by designing and implementing a “certificate” investigator training program. This program will be co-directed by the Dean of the School of Nursing, who has extensive experience in this field, and the Executive Vice President of the Urban League of Pittsburgh, who is a highly respected community leader who has co-developed successful large-scale CBPR programs with the CTSI PI. Program objectives include the development of scientists who are knowledgeable about the fundamentals of community-based research and participant recruitment, have the communication skills required for effective presentation of health information and research protocols to the lay community, are culturally sensitive, understand approaches to specific communities, and are knowledgeable about the design of health and research related public-service announcements and recruitment advertisements.

**e) Regulatory knowledge and Support-** Regulatory compliance in research conduct is critical to sustaining and transforming the University of Pittsburgh’s clinical and translational research enterprise. To achieve compliance, scientists must participate actively in regulatory compliance education. At the AHC, such programs exist--but in many fragmented silos, making investigator training suboptimal and difficult to track. The CTSI will effectively educate scientists on regulatory compliance issues by developing a centralized, well communicated institutional approach to regulatory compliance education to ensure that CTSI scientists have current and continuing regulatory knowledge. To enhance regulatory compliance, the CTSI Regulatory Knowledge and Support Core will 1) identify existing research regulatory resources and assess applicability for expansion; 2) identify regulatory compliance education and training, resources, and services gaps; 3) create new education and training programs, resources, services, and tools based on identified gaps; and 4) evaluate the effectiveness of all education and training, resources, services, and tools in the AHC.

**GOAL 3- Transformation of the Research – The CTSI will transform the conduct of research by 1) *integrating existing and being innovative in developing new crosscutting research methodologies and tools that will be incorporated into the development of clinical and translational research hypotheses, the promotion of translational science collaborations, the development of research educational initiatives, and the performance and regulation of clinical and translational research, and 2) facilitating the performance of highly innovative and***

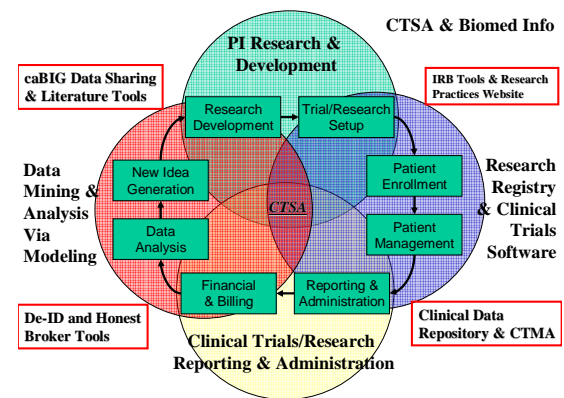
**pioneering translational research that can be rapidly developed into new disease preemption and prevention strategies, drugs, devices, diagnostics, and therapeutics and efficiently translated to humans and clinical practice.**

**Overview of Transformation of Research:** Rapid, effective translation of scientific discoveries to individuals and clinical practice will not occur solely by developing a cadre of highly trained clinical and translational scientists. Given the increasing complexities of basic science (e.g., molecular genetics, stem cell biology), severe limitations on funding, and increasing regulations governing the conduct of research, individual investigators face significant challenges in developing translational research programs. These challenges have inhibited many investigators’ creativity and limited the scope of their work by forcing them to confine their studies to those that are feasible in the context of the current research environment. The CTSI will overcome these barriers by providing institutional resources for the performance of highly innovative and pioneering translational research that can be rapidly translated into new disease preemption and prevention strategies, drugs, devices, diagnostics, and therapeutics and for the efficient and rapid translation of these discoveries to humans and clinical practice. The CTSI will accomplish these goals by *integrating* existing, and developing *innovative* new crosscutting research methodologies and tools that will be incorporated into the development of clinical and translational research hypotheses, promotion of translational science collaborations, and all aspects of the performance and regulation of clinical and translational research.

**Key Functions Conducted To Achieve Goal 3: Transformation of the Research**

**a) Center for Clinical and Translational Informatics-**

The CTSI Center for Clinical and Translational Informatics (CCTI) will “transform research” at the AHC by infusing biomedical informatics into each step in the clinical and translational research project life cycle (Figure). This goal will be accomplished by *integrating* existing biomedical informatics tools developed at the University (e.g., Clinical Trials Management Application [CTMA] developed at UPCI, De-ID©, GCRC Information Technology tools) and by outside sources and developing *innovative* advanced informatics tool kits to support the CTSI educational and translational research missions. As examples, 1) CCTI will develop an “Online Research Community” as an electronic infrastructure that will promote collaboration and transform communication, information sharing, and access to education for the AHC research community; 2) CTMA will be reconfigured to provide fiscal accountability for ALL clinical research performed at UPMC; and 3) the CTSI patient research registry, which is linked to an interoperable network of EHRs, will increase subject recruitment throughout the AHC and serve as a model for subject recruitment via EHRs at other CTSA sites. By developing these and additional “open source” tools to share with other CTSA sites, the University of Pittsburgh CTSI will connect the national clinical and translational research community by an electronic grid that will facilitate the conduct of research and develop novel modeling strategies, data mining techniques, and other innovations in service of translational research.



**b) Participant and Clinical Interactions Resources-** Clinical and translational research requires a broad range of venues to engage subjects and efficiently conduct protocols. The CTSI will transform the conduct of research at the AHC by providing resources (e.g., UPMC office-based and community locations as study sites; transportation) and transforming the Children’s Hospital of Pittsburgh GCRC and the four sites of the University of Pittsburgh GCRC. This transformation will reengineer large GCRC infrastructures into specialized models for the conduct of interdisciplinary research. For example, the CHP GCRC will be merged with extensive outpatient pediatrics research and clinical networks to serve as the home for pediatric research in western Pennsylvania and to broaden its scope well beyond that of the existing inpatient-based CHP GCRC. Similarly, the Magee-Womens Hospital GCRC site will be freed from the parent inpatient GCRC administrative structure and will serve as a model for outpatient research performed in a primary care setting. The three other sites will serve as models for interdisciplinary research, intensive research, and specialty research.

The reengineering of the GCRC administrative framework also provides an opportunity to address two shared University and UPMC missions: elimination of health disparities and improvement of community health. GCRC resources will be redeployed to pilot two innovative models for performing clinical and translational research. First, the *Braddock Minority Health Clinical and Translational Research Center (CTRC)* will be

based at UPMC Braddock Hospital in Braddock, PA, a traditionally African American community just outside of Pittsburgh. This CTRC will provide research space on a clinical unit and “floating” CTSI research coordinators to perform low and intermediate intensity clinical and translational studies. Second, *Community Practice-Based CTRCs* will consist of UPMC-affiliated primary care practices that will have full-time research presence.

**c) Translational Technologies and Resources-** The AHC is home to myriad core laboratories that support translational research in the health sciences. These service facilities have state-of-the-art equipment, trained technical support staff, consulting services, and educational resources that are widely available to investigators from across the AHC. Other organized activities at the AHC serve as more localized cores, supporting a select group of investigators, often within a specified area of research. The Translational Technologies and Resources Core will 1) establish mechanisms for assessing the translational resource needs of the CTSI research community and, in response, provide broadly needed resources by developing new core facilities; 2) develop a network of interaction between localized cores that are focused on similar services/disciplines to minimize duplication, enhance efficiency, and broaden access; and 3) develop robust mechanisms for informing the CTSI membership about core services that are available.

To inform CTSI membership about available resources and expertise; facilitate the use of these resources without undue bureaucracy; and identify needs for the development of new resources, the CTSI will develop a “Research Facilitator” program as part of its central operational structure. Research Facilitators will be health professionals (e.g., nurses; pharmacists) with extensive clinical and research experience. Facilitators will meet individually with CTSI members to provide a single point-of-service resource to:

1. Review proposals to identify specific needs for education and training; clinical, translational, and community core resources; and regulatory education and assistance; eligibility for pilot, collaborative, and novel methodologies funding programs; and opportunities for collaboration and commercialization.
2. Contact appropriate core lab/services directors; community liaisons; potential collaborators; and grant sponsors to confirm synergies and initiate collaborative interactions. An emphasis will be placed on promoting the use of existing and newly developed institutional participant recruitment resources.
3. Identify resource needs that are suitable for development as emerging novel CTSI core resources.

The Research Facilitator program will enhance the growth, efficiency, and speed of clinical and translational research by substantially reducing investigator and staff time commitments to identification and arrangement of collaborative efforts and use of core resources. To further improve this process, the CTSI Center for Clinical and Translational Informatics will develop an interactive web-based database that can provide facilitators with a current list of available resources and informatics tools to track investigator flow through CTSI cores.

The CTSI recognizes that the geographically dispersed distribution of the AHC requires that this program needs to provide efficient access to members who are not based on the main campus. Despite an elaborate network of shuttle buses, scientists at the new Children’s Hospital campus; the University of Pittsburgh Cancer Institute; Magee-Womens Hospital; the McGowan Institute for Regenerative Medicine; and remote UPMC hospitals need to have more access to this program. The current geographic barrier is of particular concern to junior investigators who are unfamiliar with the complexity of sites and logistics associated with clinical research. Accordingly, the CTSI will develop a “Virtual Research Facilitator” program with two features:

1. A web-based portal for scientists to submit project information that can be used by Research Facilitators to initiate the process outlined above
2. Use of the IRB’s new electronic submission system to identify investigators’ potential research resource needs using an automated algorithm. This algorithm will generate an email notification that contains a “menu” of relevant resources with contact information.

**d) Development of Novel Clinical and Translational Methodologies-** The development of novel methodologies is critical to achieving the CTSI’s goal of *transforming research*. The CTSI Novel Clinical and Translational Methodologies Core will develop novel methodologies, approaches, and technologies that 1) have wide impact on the broader translational and clinical enterprise; and 2) focus on facilitating the linkage of data and concepts from a wealth of sources. This core will identify, fund, and develop novel translational research approaches, technologies, and methods and promote their use by a wide range of CTSI members. Two specific novel programs will be developed during the first three years of funding. Subsequent years will solicit proposals for the development of additional novel clinical and translational methodologies.



During the first three years of funding, the CTSI will develop clinical and translational applications of novel software. “Diamond” is an open-source software system jointly created by Intel Research and Carnegie Mellon University that provides architecture to perform efficient *interactive distributed searches* for rapidly scanning large volumes of distributed data and filtering that data with domain-specific software. This software has been successfully used to search for vaguely-specified items in many terabytes or petabytes of complex and loosely-structured data like digital photographs and video streams. In the Novel Clinical and Translational Methodologies Core, innovative Diamond tools (*Interactive Search-Assisted Diagnosis*) will be developed as new approaches to medical diagnoses. The program will create and validate Diamond applications that embody domain-specific knowledge relevant to the diagnosis of breast lesions using mammograms and pathology images. The goal of this novel program is to efficiently and effectively search for (identify) suspected breast mass regions depicted on either mammograms or pathological images that are visually similar to the queried mass region from two large, diverse radiographic and pathology reference libraries. If successful, this approach will have broad applicability to many other diagnostic contexts that involve extensive use of imaging.

A second program will develop an institutional patient research registry for subject recruitment by integrating the >50 electronic health record (EHR) systems across the >350 UPMC outpatient locations and 19 hospitals. This program will employ electronic patient registration systems to automatically generate IRB-approved consent forms that seek approval from all UPMC outpatients (~3,000,000 visits/yr) to be contacted for the purpose of recruitment into research studies. After consent is obtained, the EHRs will be automatically queried to match patient demographic and clinical information with study inclusion and exclusion criteria. The result will be the generation of lists of potential subjects who will be contacted for the purposes of study recruitment. A modified registry system will be developed for use at community locations (e.g., pharmacies; churches; schools). This system will also provide capabilities for adverse event reporting and fiscal reconciliation.

**e) Design, Biostatistics, and Clinical Research Ethics-** As described under “Transformation of the Scientist,” this core will offer technical assistance throughout the entire research process from concept through study design, analysis, and dissemination by providing expert consultations on research methodology, measurement adaptation and evaluation, form design, data management and analysis. In addition, the core will perform methodological work on novel clinical and translational study design and statistical methodologies.

**GOAL 4. Transformation of Health Practice – The CTSI will transform regional health practice by building a “population-based laboratory” through collaborative community-based participatory programs to generate research hypotheses and develop and test new collaborative methods for translation of basic and preclinical scientific discoveries to health practice in western Pennsylvania.**

**Overview of the Transformation of Health Practice:** As noted in the introduction, biomedical research must overcome two “Valleys of Death” before it is effectively translated to health practice<sup>2</sup>. Whereas most CTSI programs will focus on increasing the speed and efficiency of translating basic biomedical discoveries to clinical research, substantial efforts will also be dedicated to incorporating research findings into health practice. Elements that are critical to achieve this goal include the existence of 1) scientists with advanced training in the translation of research findings to clinical practice; 2) extensive networks of multidisciplinary “research-informed” health professionals who embrace evidence-based practice (EBP) and actively participate in the research process; and 3) a “research-informed” community of patients and members of the general public who demand incorporation of state-of-the-art research findings into their health care. The CTSI will develop these components as described below.

#### **Key Functions Conducted To Achieve Goal 4: Transformation of Health Practice**

**a) CTSI Research Education, Training, and Career Development Program-**The CTSI T32 “Translating Research into Practice Doctoral Program” (TRIP PhD) will train scientists to develop and apply new methodologies of translating research into health practice. This program will emphasize the training of scientists with a foundation for applying technological advances (e.g., informatics, information technology, internet, Electronic Health Record, hand held devices, smart cards) to the processes of translating research into practice. CTSI will coalesce and transform three strong, existing programs to create the more innovative TRIP doctoral program; these three programs are: the University of Pittsburgh Biomedical Informatics PhD program, the CMU Human Computer Interaction Institute PhD program, and the University of Pittsburgh Institute for Clinical Research Education Certificate and MS degree programs in Clinical Research. Core courses will be used as a springboard for possible dissertation projects; a requirement of such projects will be a central focus on health care transformation that translates research into practice.

**b) Community PARTners Program-** This Core will play a key role in developing “research-informed” health professional and lay communities that embrace and actively participate in the conduct and translation of research. This goal will be accomplished by meaningfully involving each of these communities in the setting of research priorities, the mentoring of junior investigators, and the development of, and access to, educational and service resources. As an example, the Evidence Based Practice (EBP) foundation of the School of Nursing curriculum will be used to develop an EBP program in multidisciplinary UPMC community outpatient practices. This program will include continuing education on the EBP model, identification, funding, and training of staff EBP resources, provision of an EBP toolkit, and a longitudinal educational program that focuses on the application of evidence that pertains to practice. As an example of a service initiative, the CTSI will establish a continuity screening program in the office of a respected community organization, the Urban League of Pittsburgh, to engage a cohort of laypersons who are committed to participation in research studies and who will serve as community ambassadors for clinical and translational research.

**c) CTSI Administration: Development of a Matrix of Health Professional Networks-** To translate research on a regional scale, it is critical that the CTSI develop a network of health professionals who are committed to incorporating innovative research into health practice. This goal will be accomplished by capitalizing on UPMC’s extensive and geographically distributed clinical networks. These networks are woven into the communities of 29 western Pennsylvania counties and provide comprehensive clinical care, and, via the UPMC Health Plan insurance portfolio, the ability to rapidly incorporate translational research findings into health policy. Traditionally, these decentralized networks have been oriented around (1) medical specialties (e.g., UPMC Cancer Centers; Magee-Womens Hospital Womancare Centers; CHP Children’s Community Practice Network); (2) disciplines (e.g., nursing, rehabilitation, dental medicine); (3) points of service (e.g., School of Pharmacy/Rite-Aid community pharmacy partnership); and (4) populations (e.g., Center for Rural Health Practice at University of Pittsburgh Bradford campus, GSPH Center for Minority Health). The CTSI will transform the AHC by centralizing these extensive networks in an innovative integrated matrix through CTSI’s administrative and informatics efforts. This matrix will be made accessible to CTSI investigators to foster the generation of translational research hypotheses, facilitate the performance of clinical and translational research studies, recruit large numbers of diverse study subjects, and directly translate research findings and biomedical discoveries to clinical practice. These goals will be accomplished by identifying a leadership team within each network to interact with CTSI investigators through the CTSI Research Facilitators. The CTSI will have quarterly meetings of network leadership teams, provide virtual linkage through a web-based portal and web casts, and will organize unifying continuing education activities through Center for Continuing Education, Health Sciences. Each network will be required to:

- 1) Identify clinical activities, quality initiatives, clinical research, educational and screening programs, and community outreach that are performed by network providers
- 2) sustain a cohesive network through common educational initiatives (e.g., EBP; CTSI community-based educational and screening programs) and translational informatics (e.g., electronic health record, CTSI institutional research registry)
- 3) provide point of service access to CTSI investigators to serve as a focal point for (a) development of research collaborations between network health professionals and CTSI investigators, (b) recruitment of study participants, (c) network-based performance of clinical research studies, (d) translation of CTSI investigators’ research findings and discoveries into clinical practice, (e) development of clinically relevant research hypotheses to be studied in the CTSI, and (f) identification of existing or newly developed barriers and resource needs for clinical and translational research.

**c) CTSI Catalyst Program-** Translation of biomedical discoveries to practice frequently requires collaboration between scientists and industry professionals. The CTSI Catalyst Program will 1) promote training of students and faculty to advance understanding of the partnership between AHCs and industry that promotes the development of novel therapeutics and diagnostics, and 2) create strategic interactions between CTSI members and industry. This latter aim will be achieved by facilitating interactions between CTSI members and the Office of Enterprise Development, Health Sciences (OED) and by providing targeted pilot funding to promote the development of commercially viable products. OED provides innovative technology transfer and commercialization programs that center on the inventor, not the invention, and spawn new institutional collaborations with industry partners. CTSI members will have access to these partnerships to accelerate the development of novel drugs, diagnostics, and devices.

## **CTSI GOVERNANCE, ADMINISTRATION AND STRUCTURE**

Historically, the University of Pittsburgh has an extensive track record of clinical and translational science that

has transformed the prevention (e.g., polio vaccine), diagnosis (e.g., Pittsburgh Compound B for Alzheimer's Disease), and treatment (e.g., liver transplantation, breast cancer surgical and adjuvant treatment) of diseases worldwide. These examples have a common foundation: Each was the result of the efforts of a multidisciplinary team of basic and clinical scientists that investigated a hypothesis generated by a clinical observation or need. Over the past two decades, however, a number of major scientific advances have been led by basic scientists performing "curiosity driven" research aimed at understanding the fundamental workings of the cell and the molecule rather than combating a specific disease. Although these discoveries will undoubtedly prove to be essential to understanding numerous disease processes and, ultimately, to achieving the goals of disease preemption, prevention, diagnosis, and treatment, this new knowledge will not achieve its full potential application until it is translated to humans and health practice by multidisciplinary teams of clinical and translational scientists. This translation will require that scientists of all types—basic, translational, clinical, behavioral, population-based—consider the broadest possible implications of their work and team with members of other disciplines to maximize the human health impact of their findings. The University of Pittsburgh is committed to catalyzing changes in the scientific enterprise by serving as a model for the transformation of scientific culture, environment, and institutional structure to develop clinical and translational science as a distinct discipline through the formation of the CTSI. This transformation will result in fundamental changes in the *institution*, training of *scientists*, performance of *research*, and *health* practice.

The CTSI is uniquely positioned to serve as a model for the transformation of clinical and translational research. The CTSI's governance and administrative structure; broad institutional authority; integration with a health system that has ≈50% market share and a regional health insurance plan; and partnerships with RAND and CMU provide it with the ability to develop a regional academic home for clinical and translational scientists that fosters a collaborative multidisciplinary culture and nurtures the generation and testing of innovative, bidirectional (from lab to human to population and vice versa) hypotheses by interdisciplinary teams. The CTSI will develop as a distinct interdisciplinary entity external to any individual school, department, division, center, and program. This framework will guarantee the development of clinical and translational science as an independent and respected discipline within the AHC, which would not be possible if the organization of the CTSI was limited to traditional departmental status within a single school.

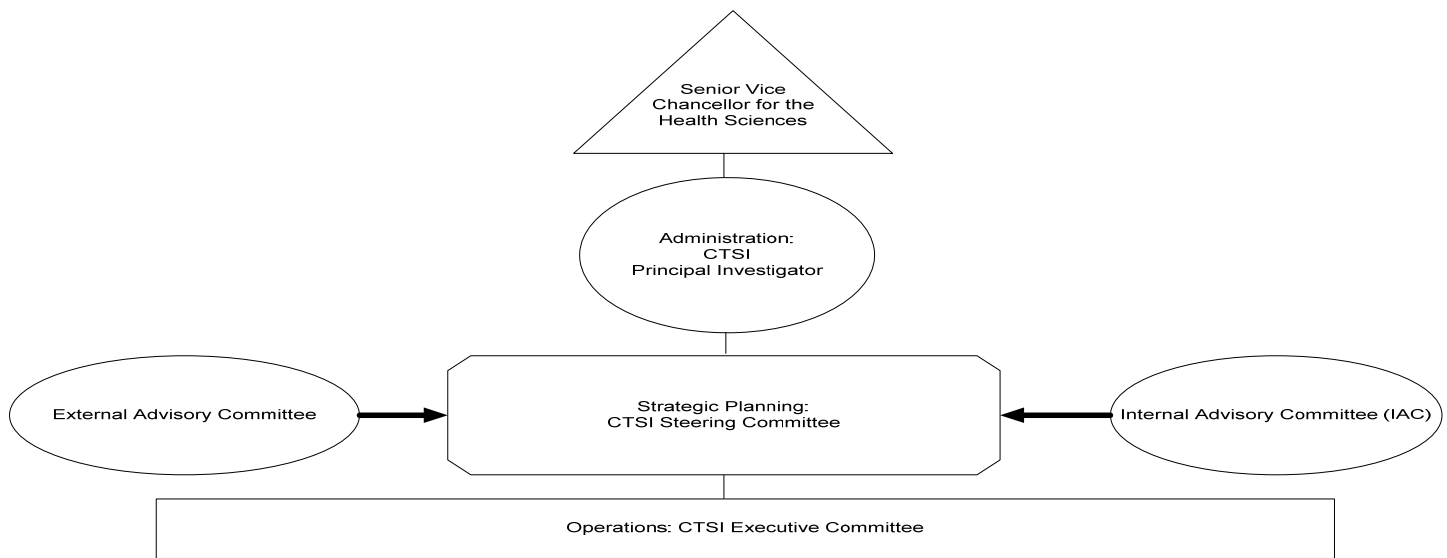
To achieve its transformative goals, the CTSI will have:

- Structure, governance, available faculty, and transcendent institutional authority across the health sciences to create and maintain an innovative and integrated program resulting in an institute that fosters an environment in which both research and researchers flourish.
- An administrative structure that anticipates and effectively responds to investigators' and trainees' needs.
- Dedicated physical space for faculty and trainees.
- A recruitment plan for new investigators and research programs.
- A mechanism to evaluate and replace program directors.
- Accountability for the structure, function, and budget of the institute.
- A mechanism to award institutional credit to component directors.
- A systematic approach to continuing evaluation of the quality, productivity, and equitable distribution of resources.
- A process to address underutilization, inappropriate use, low productivity and other problems.

CTSI structure, governance, and administration that will address these characteristics are described below:

### **Structure, Governance, Available Faculty, and Transcendent Institutional Authority**

**(1) CTSI Structure and Governance-** The CTSI will have a three-level governance structure comprising Administration, Strategic Planning, and Operations. This structure is designed to foster an environment in which both research and researchers flourish.



## (2) Leadership

(a) **Leadership/Administration:** The University of Pittsburgh Associate Vice Chancellor for Clinical Research, Health Sciences, Steven E. Reis, MD, will serve as the **CTSI principal investigator** and founding Director. Dr. Reis' existing transcendent responsibilities for clinical research across the health sciences schools provide him with institutional authority to implement the CTSI Roadmap as outlined in this application. This authority has been conferred by the SVCHS, Dr. Arthur S. Levine, and University Chancellor Mark A. Nordenberg (see letters of support). As principal investigator, Dr. Reis will have institutional responsibility for the CTSI, which includes oversight of: 1) CTSI academic, administrative, strategic, and fiscal functions, 2) collaborations with other CTSA sites to adopt and implement measures established by the CTSA National Committee, 3) provision of information to the NIH Program and Science Officers, and 4) maintenance of institutional career development opportunities for recruiting and encouraging new investigators to work in clinical and translational science. Dr. Reis will oversee the Administrative Director for Grants and Contracts and the Administrative Director of Operations, who will be responsible for CTSI fiscal and operational issues, respectively. The Administrative Director for Grants and Contracts will co-report to the Associate Senior Vice Chancellor for Administration, Health Sciences. This co-reporting structure ensures CTSI's fiscal independence.

Dr. Reis is particularly well qualified to play this central leadership role since in addition to his administrative responsibilities and experience as Associate Vice Chancellor for Clinical Research, he is also an established, nationally-renowned clinical and translational scientist with an active research program focusing on the epidemiology, pathophysiology, and genetics of gender and race-related differences in cardiovascular disease (CVD). He is Professor of Medicine and Emergency Medicine, Director of the LHAS Women's Heart Center at UPMC, and a member of the American Society for Clinical Investigation. He serves(ed) as principal investigator for 1) the NHLBI Women's Ischemia Syndrome Evaluation Study at the University of Pittsburgh; 2) NHLBI RO1s studying the pathophysiology of CVD and hormones in women; and 3) the Commonwealth of Pennsylvania-sponsored multidisciplinary CBPR project, "Heart Strategies Concentrating on Risk Evaluation," designed to reduce racial disparities in CVD. He has an established mentoring record and is a co-mentor for one of the first CRSP Scholars in the University's Roadmap K12 program. These qualifications demonstrate that Dr. Reis has the background and experience to define the CTSI's direction, identify investigators' and trainees' needs, and recruit new investigators and research programs.

The CTSI will have Institute Co-Directors to cover each of its 4 key elements (Figure):

- 1) **Education and Career Development-** *Wishwa N. Kapoor, MD, MPH* is Falk Professor of Medicine and Health Policy and Management, Director of the Center for Research on Health Care, Chief of the Division of General Internal Medicine, and Founding Director of the University of Pittsburgh K30, Roadmap K12, and CSTP Clinical Research Training Programs. He is a member of the American Society for Clinical Investigation and the Association of American Physicians and is an internationally recognized expert in clinical research focused on clinical epidemiology and health services. His areas of expertise include multidisciplinary studies of common medical problems such as syncope and community-acquired pneumonia.
- 2) **Translational Research-** *Robert A. Branch, MD* is Professor of Medicine and Pharmacology and an internationally recognized clinical pharmacologist whose main research has been on intersubject variability

and mechanisms of regulation of drug metabolism in humans. Dr. Branch is Director of the Center for Clinical Pharmacology and leader of the Pharmacogenomics Drug Metabolizing Program. His ability to conduct and train scientists in the performance of translational research is facilitated by his role as Program Director of the NIH-funded University of Pittsburgh General Clinical Research Center (GCRC).

3) **Clinical Research-** *Steven E. Reis, MD* will serve as both PI and Co-Director for the Clinical Research-related cores. His qualifications as Co-Director are described above.

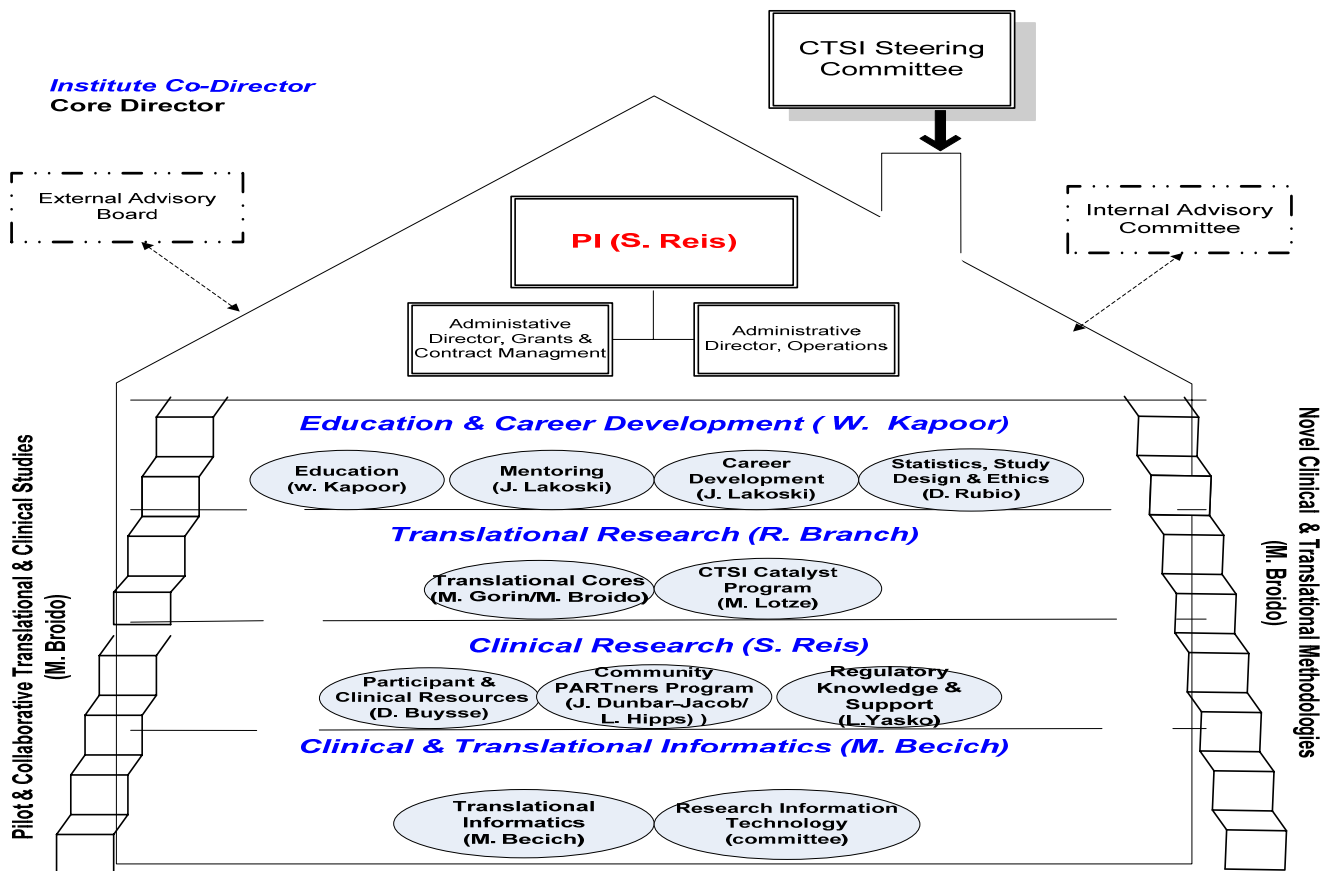
4) **Clinical and Translational Informatics-** *Michael J. Becich, MD, PhD* is Professor of Pathology and Information Sciences and Telecommunications and serves as the Director of the Center for Pathology Informatics and Vice Chair of Pathology Informatics. He served as Director of the UPCI's Benedum Oncology Informatics Program and led the Anatomic Pathology Lab Information System (LIS) team that developed and implemented two imaging systems that integrated 19 UPMC hospitals onto a common LIS platform. His research interests are in cancer biology and biomedical informatics as applied to Pathology and Oncology and his work focuses on developing applications and databases to manage the analysis of expression data derived from high throughput genomics. His laboratories are funded by the NCI, NCRR, NIDDK, and the Pennsylvania Dept. of Health. He leads the University of Pittsburgh's efforts in the NIH Cancer Biomedical Informatics Grid (caBIG) program. As a result of his accomplishments, Dr. Becich was recently appointed as the founding chair of the Department of Biomedical Informatics in the School of Medicine.

(b) *Strategic Planning:* The **CTSI Steering Committee** will be responsible for 1) strategic planning; 2) addressing operational issues and proposals developed by the operational CTSI Executive Committee; and 3) developing and implementing substantive plans in response to the results of the formal CTSI Evaluation Program. This latter function will be supported by the Steering Committee's ability to modify, develop new, or deactivate CTSI cores and components based on objective evaluations of utilization, productivity, quality, and dynamic changes in investigators' and trainees' needs. As outlined in **Table 2**, the Steering Committee will be composed of the CTSI PI (chair), Institute Co-Directors, the deans of each of the six schools of the health sciences, and the Senior Vice President, Quality Care and Chief Medical Officer of UPMC. During the first 12 months, meetings will occur biweekly to develop the details of, implement, and modify CTSI initiatives and to evaluate progress toward implementation. Frequency of meetings beyond the first 12 months will be determined based on progress and identified need. The Committee will meet monthly with the multidisciplinary CTSI Internal Advisory Committee for the first 12 months and at least quarterly thereafter. The Steering Committee will also meet or teleconference with the CTSI External Advisory Board quarterly for the first 12 months, including an onsite meeting coinciding with the annual CTSI "Synergies in Health Sciences Research Day." Subsequent meetings of the External Advisory Board will occur at least semi-annually.

(c) *Operations:* In addition to serving on the CTSI Steering Committee, each Co-Director will be responsible for the operations of several CTSI cores. In turn, each core will have a "Core Director" who will be responsible for daily operations, as described in specific sections of this application. Given the spectrum of responsibilities and scopes of the diverse CTSI cores, it is critical that the Core Directors interact regularly as the **CTSI Executive Committee** to 1) collectively address training, education, career development, resource support, and recruitment issues as they pertain to CTSI Scholars and members; 2) identify utilization, productivity, quality and resource distribution issues; 3) discuss common administrative and financial issues; and 4) develop joint initiatives to further the CTSI mission. The Executive Committee will also include the CTSI PI, Institute Co-Directors, and Administrative Directors. The Executive Committee will meet weekly for the first six months and then at least monthly.

(d) *Internal Advisory Committee-* As the academic home for clinical and translational science, the CTSI will firmly establish "interdisciplinary" research as its central theme, which requires multidisciplinary investigators to collaborate in all aspects of clinical and translational research and training. To ensure that the CTSI is optimally promoting these efforts and is addressing issues of relevance to investigators throughout the AHC, a multidisciplinary **Internal Advisory Committee (IAC)** will be formed to guide the CTSI Steering Committee. The IAC will consist of senior and junior translational scientists from each health sciences school, CTSI Scholars, respected community leaders, representatives from corporate Pittsburgh, a RAND designee, and senior UPMC administrators (see Table 3). The IAC will advise the Steering Committee on strategic direction and will review results of the CTSI evaluation process and the CTSI response to evaluations. Meeting frequency is described above.

(e) *External Advisory Board-* An **External Advisory Board** will be formed in accordance with directives from the NIH Program Office. Meeting frequency is described above.



### **Providing Appropriate Institutional Credit To Component Directors**

The CTSI PI, Co-Directors, and Core Directors will dedicate substantial effort to the Institute. These efforts must be rewarded beyond salary support. The SVCHS will ensure that this occurs by guaranteeing protected time for actual effort and by requiring each health sciences school to incorporate service as a CTSI Co- or Core Director in its annual faculty reviews, promotions and tenure processes, and financial compensation models. This commitment represents strong institutional support for the role of CTSI leaders in training and supporting future leaders and scientists in the discipline of clinical and translational science.

### **Process of Evaluating and Replacing Program Directors, and Accountability for the Structure, Function, and Budget of the Program**

The CTSI Steering Committee will provide an annual report to the SVCHS. This report will include: 1) previously submitted one-, three-, five-, and ten-year goals of the institute; 2) progress made toward achieving these goals, 3) summary of internal and RAND evaluations of the CTSI and its components, 4) descriptions of actions taken in response to evaluations, 5) complete financial reports, 6) report from the External Advisory Board, and 7) revised one-, three-, five-, and ten-year goals. Progress reports will also include descriptions of achievements made by each CTSI core, with a particular emphasis on training, faculty development, and institute productivity. Special note will be made regarding the CTSI's contribution to the National CTSA Consortium and the CTSI's adoption of best practices identified by other CTSA sites. The SVCHS will review this report and consider feedback from the External Advisory Board. Based on these deliberations, the SVCHS will make an annual determination of the institute's progress that will be submitted to the NIH Program Officer. The SVCHS has the authority to replace the CTSI Co-Directors and Senior Administrators.

**(3) Availability of faculty-** Previously described under **“Faculty, Staffing and Direction of the CTSI”**

### **Creating and Maintaining an Innovative and Integrated Program, and Fostering an Environment in Which Both Research and Researchers Flourish**

In 1952, an interdisciplinary research team led by Dr. Jonas Salk developed the polio vaccine at the University of Pittsburgh. Within *three* years, this biomedical breakthrough was translated from the laboratory to humans and incorporated into clinical practice and health decision-making. This example highlights a fundamental principle of the CTSI: effective and *rapid* translation of innovative interdisciplinary research requires the

coordinated efforts of a highly-trained, collaborative, multidisciplinary research team. It is well-established that scientific creativity depends on collaborative communication. Scholars of the sociocultural process of creativity often report that 1) groups are more creative than individuals; 2) "scientific progress is a cooperative group effort, involving...important contributions from each of a group of professionals"; and 3) "scientific discovery happens through intensive social interaction in laboratories and universities, not through isolated bursts of insight by a few great individuals"<sup>5</sup>. A major CTSI priority is to create and foster an environment that instills the value of collaboration and communication among junior investigators and to promote the creation of creative multidisciplinary clinical and translational research teams. This environment will provide formal, informal, and "virtual" structures that bring and hold scientists together; support education, training, and career development of scientists engaged in interdisciplinary work; establish and maintain strong interdisciplinary linkages; foster teambuilding to generate interdisciplinary research hypotheses; and provide institutional support for multidisciplinary collaboration in interdisciplinary clinical and translational research.

In a traditional academic *medical* center, collaboration can be promoted by using centrally-located space to provide education, career development, and institutional research resources programs and as a location for the performance of clinical and translational research. However, this approach will limit the success of the research enterprise in a large AHC that has well-established existing research centers of excellence interspersed with a geographically distributed clinical operation (urban, suburban, rural). In addition to geographic challenges, large AHCs also have a problem with the temporal "disconnect" that exists as a result of clinical researchers and clinicians having schedules that revolve around patients and basic scientists having schedules that revolve around laboratory experiments. These issues must be addressed in the CTSI space plan.

### **Physical Space Available for Faculty and Trainees**

To address the challenges described above, the CTSI will use dedicated central and geographically dispersed physical and "virtual" space to serve as a nidus for clinical and translational researchers to interact to promote interdisciplinary collaboration; to support academic career development and educational programs; and to increase the speed and efficiency of clinical and translational research. Space development will require a stepwise multifaceted approach that may be modified over time by the CTSI Steering Committee as a result of longitudinal evaluation processes. As described below, Phase 1 (2006-9) of the CTSI space plan will integrate and redesignate existing space as CTSI resources. During Phase 2 (2009-2011), CTSI administration, key functions, and relevant central cores and programs plan to move into a renovated facility that will serve as the academic home of clinical and translational science in western Pennsylvania.

#### **(1) Phase 1 (2006-2009): Integration of Geographically Dispersed Clinical and Translational Research Facilities**

**(a) Dedicated Space for the CTSI Center for Clinical and Translational Research Education:** The SVCHS recently renovated 12,009 sq. ft. of space to serve as the dedicated home for clinical and translational research education. The fact that this facility is separate and independent of the individual health sciences schools, departments, and divisions has contributed to its established success in attracting scholars from all six schools into the existing Roadmap K12 and K30 training programs. In addition to housing these programs in the CTSI, this space will serve as the central hub for the CTSI T32 and doctoral programs. To address the AHC's geographic dispersion, the CTSI will rotate its other educational programs among the health science facilities and satellite campuses to maximize the probability of interactions among investigators and health practitioners from different disciplines. These more frequent interactions are expected to lead to an increased number of collaborations<sup>5,6</sup>. The CTSI evaluation process will collect data on the number of interactions and collaborations that develop, and these results will guide the CTSI Steering Committee's development of a strategic plan for locations for future educational initiatives.

**(b) Dedicated Home for CTSI Administration, Research Facilitator Program, and Clinical and Translational Research Networks** – During Phase 1 of the CTSI space plan, the administrative hub (2554 sq. ft.) will be in the SVCHS suite. This central location is adjacent to the six health sciences schools; five UPMC hospitals (Presbyterian University Hospital; Eye and Ear Institute; Western Psychiatric Institute and Clinic; Children's Hospital of Pittsburgh [existing]; and Montefiore University Hospital); and the majority of core laboratories and facilities. Accordingly, it is ideally suited to provide physical space for CTSI administration and the Research Facilitator and Clinical and Translational Research Networks programs. In addition, this facility will serve as the administrative home for fiscal affairs and operations and several key CTSI functions, including: Pilot and Collaborative Clinical and Translational Studies; Novel Clinical and Translational Methodologies; Translational Technologies and Resources; components of the Center for Clinical and Translational Informatics; and educational initiatives targeting broad audiences (e.g.; Research Coordinator Orientation, Clinical Research Seminar Series). Because of its central location in the city of Pittsburgh, the

CTSI administrative hub will also serve as the center for the University's component of the CTSI Community PARTners Program (the community base for this initiative will be located within ~two miles of the CTSI).

(c) **Dedicated Space for CTSI Cores:** During Phase I of the CTSI space plan, existing facilities that house CTSI key functions will be administratively linked to form the integrative CTSI (see below). The CTSI Clinical and Translational Research Centers (CTRC) will, by design, be geographically distributed to capitalize on the existence of specialized translational research centers of excellence (e.g., University of Pittsburgh Cancer Institute; Children’s Hospital; Magee Womens Hospital; Western Psychiatric Institute and Clinic). For other CTSI components, space will be allocated in the Phase 2 CTSI facility plan based on the Steering Committee’s interpretation of the evaluations performed during Phase 1.

**Phase I Space Plan (2006-9)**

<b>CTSI Program</b>	<b>Space</b>	<b>Location</b>	<b>Purpose</b>
CTSI Administration	2,554 sq. ft.	Office of Senior Vice Chancellor for Health Sciences	CTSI administration, Research Facilitators, CTR Networks, Pilot Studies; Novel Methodologies, Translational Resources
CTSI Center for Clinical and Translational Research Education	12,009 sq. ft.	Institute for Clinical Research Education	CTSI K12 & K30, CSTP, new T32 program
CTSI Office of Academic Career Development	703 sq. ft.	Office of Senior Vice Chancellor for Health Sciences	Academic career development & mentoring for CTSI Scholars
Clinical and Translational Research Centers (CTRC)	9,454 sq. ft. (current) 9,965 sq.ft. (committed) 6,626 sq.ft. 5,234 sq. ft. 983 sq. ft.  800 sq. ft  2,352 sq.ft.	UPMC Montefiore  Magee Womens Hospital WPIC Children’s Hospital of Pittsburgh UPCI Hillman Cancer Center UPMC Braddock	Research “intensive care” CTRC Women’ specialty CTRC Neuroscience CTRC Pediatric CTRC  Oncology CTRC  Community-based CTRC
CTSI Translational Informatics	26,000 sq. ft. 12,000 sq. ft. 40,000 sq. ft. (committed)	U. Pgh. Cancer Institute Parkvale Building Biomed. Science Tower 4	Translational Informatics

(d) **Development of a Virtual Home for Clinical and Translational Research:** To address barriers to fostering interdisciplinary collaborations due to geographic and temporal disconnects, the CTSI will develop IT-based initiatives to provide education, foster collaborations, and facilitate resource use. For example, the CTSI Center for Clinical and Translational Informatics will provide capabilities for distance education for both synchronous and asynchronous instructional events using systems like interactive television (ITV); Mediasite®; RealSystem Server 8®; and a wide range of and Tele-educational initiatives (e.g., educational web pages; imaging capable LIS; TV teleconferencing based dynamic systems; static robotic systems; whole slide imaging; tele-consultation; tele-mentoring)7. The resulting program will serve as a virtual home for clinical and translational research education. The CTSI will also build an online research community to help meet communication, information sharing, and education needs for CTSI members and the research community at large. This concept builds on a recent grant for a global dental informatics research community awarded to the University’s Center for Dental Informatics by the National Library of Medicine. The two core elements are: (1) comprehensive, information-rich directories of people, research interests, projects, services (e.g. statistical and computational), funding opportunities, and other research-related entities, and (2) intelligent information routing that both “pushes” information to and “pulls” information from community members in order to foster the development, execution, and dissemination of research projects. Information representation in the online research community will be undergirded by a controlled vocabulary (e.g., Unified Medical Language System) in order to represent information in the system in a standardized way.





(2) **Phase 2 (2009-2012)**- Through a collaborative effort between the University of Pittsburgh's SVCHS and the UPMC President, plans are being developed to renovate the existing Children's Hospital inpatient facility. These plans will include  $\approx 100,000$  sq. ft. of space for an integrative home for the CTSI (figure; see letters of support). This facility will become available  $\sim 2009-2010$  after the new Children's Hospital clinical and research complex is completed. The renovated space is centrally located in the vicinity of the health sciences schools, is connected to UPMC Presbyterian and Montefiore Hospitals, the Eye and Ear Institute, and WPIC, and is six blocks away from MWH. Regularly scheduled shuttles will connect the CTSI campus with the University of Pittsburgh Cancer Institute, UPMC Shadyside, UPMC Southside, UPMC St. Margaret's Hospital, and the McGowan Institute for Regenerative Medicine. This space will enable centralization of key CTSI components, including administration; Education, Training, and Career Development; relevant components of the CTSI Center for Clinical and Translational Informatics; central CTIC administration; and several other key functions. The descriptions of existing space in the Phase 1 space plan will serve as a template for the planned CTSI facility. However, these plans are dynamic and will incorporate results of longitudinal evaluations of Phase 1 of the CTSI space plan (2006-2009).

### **Recruitment of New Investigators and Research Programs**

The recruitment of new investigators to the CTSI requires a twofold approach that concentrates on recruitment of 1) current faculty with strong interests in transforming their academic careers to focus on interdisciplinary translational research; and 2) scientists who are being recruited to the AHC. The CTSI will take a stepwise approach to recruiting established basic and clinical scientists by providing: 1) exposure to the discipline of clinical and translational science that stimulates traditional scientists to "think outside the box" of their traditional disciplines (see below); 2) mechanisms to facilitate collaborations and multidisciplinary team building as previously described; 3) funding opportunities for pilot and collaborative interdisciplinary translational studies; and 4) facilitation of research implementation through the CTSI Research Facilitator Program and CTSI cores. To catalyze interest in clinical and translational research, the CTSI will sponsor several campus-wide programs to provide exposure to the discipline and stimulate collaboration and communication among scientists. The hallmark program will be an annual regional celebration of clinical and translational science, "Synergies in Health Sciences Research," based on the successful University of Pittsburgh "Science Day." "Synergies Day" will be a two-day event that incorporates endowed lectures (e.g., Tisherman Lecture on Health Care Ethics), presentations by nationally prominent keynote speakers, and concurrent seminars and workshops on topics as diverse as recent discoveries in clinical and translational science, interdisciplinary team building, research technologies, and regulatory and practical patient oriented research issues. Several sessions will target CTSI scholars (e.g., mentoring, promotions and tenure, women in science) and will be used to announce new Pilot and Collaborative Studies RFAs. Previously funded CTSI pilot grant awardees and CTSI scholars will be required to present their progress in oral and poster presentation formats. The SVCHS will mandate that the health sciences deans limit their schools' scheduled activities during "Synergies Day" so that the majority of their faculty and students can participate. It is anticipated that Synergies Day will become an integral part of the University's culture and will catalyze interest and collaborative efforts in interdisciplinary translational research.

As the CTSI leadership met with department chairs and deans across the health sciences during the CTSI planning process, it became clear that CTSI education, training, career development, and other programs and CTSI cores will serve as major resources for current faculty. In addition, it was noted that the development of CTSI as the institutional home for clinical and translational science provides an opportunity to attract new faculty who are seeking an environment that will support their career development as interdisciplinary researchers. The promotion of CTSI programs as a faculty recruitment tool is not unprecedented: Several department chairs have promoted the existing Roadmap K12 CRSP to attract, recruit, and retain outstanding clinical and translational scientists. This approach to faculty recruitment will also be used to recruit new research programs. In addition, the CTSI will provide competitive funding to support the development of novel clinical and translational methodology programs ( $\$100 -150,000/\text{yr}$ ) and new translational core labs ( $\sim \$100-150,000/\text{yr}$ ). Smaller programs will be supported by pilot and collaborative study grants. Applications for these programs will be generated by CTSI RFAs. All funded programs must be interdisciplinary, support or perform research by multidisciplinary collaborative teams, and have high potential for leveraging CTSI resources.

### **Anticipating and Responding to the Needs of Investigators and Trainees**

"Synergies Day" will provide an opportunity to assess the needs of investigators and trainees. During Synergies

Day, the CTSI will conduct focus groups of 1) CTSI Scholars; 2) CTSI members; 3) CTSI affiliates; 4) research staff; 5) health professionals; and 6) community representatives. The CTSI Steering Committee will analyze the focus group results to determine and prioritize needs for new initiatives, resources, programs, and funding mechanisms. The Steering Committee will then charge the CTSI Executive Committee with developing and implementing plans in response to prioritized investigator and trainee needs. Priority areas include issues related to trainees, education, career development, subject recruitment, pilot funding opportunities, translational informatics tools, community needs, and resources that can be used by large numbers of investigators. Funds can be reallocated and additional funding requests can be made by the Steering Committee to implement these initiatives. In addition to these organized focus groups, individual CTSI members can request specific resources by submitting proposals to the Steering Committee.

### • **Systematic Approach To Continuing Evaluation of the CTSI**

Given the size and complexity of the CTSI and the extent to which it will transform the institution, its scientists, research, and health practice, it is critical to systematically evaluate all aspects of the CTSI and its components. The CTSI Evaluation Program, in partnership with RAND, will develop and implement a longitudinal formative and summative evaluation program that will provide outcomes data such as quality, productivity, and achievement of objectives of the CTSI, leadership, core programs and resources, members, and stakeholders. The CTSI Evaluation Program's approach, which uses a Logic Model evaluation process, is based on the experience of its Director as the chair of the Evaluation Liaisons Committee across the 12 Institutions funded for the Roadmap K12. While other models exist for evaluation (e.g., logical framework, cluster evaluation, and case study), the logic model offers the best approach for tracking measures within programs over time and monitoring changes in performance for different comparison groups. The logic model offers flexibility to adapt the evaluation strategy as the activities and/or outcomes change. In creating a transformative CTSI, it is anticipated that adjustments will need to be made. The logic model will reflect those changes and yield useful data without compromising the overall evaluation strategy. The primary goal of the evaluation program is to identify ways to improve the CTSI (Formative evaluation). The secondary aim is to measure the impact of the CTSI on clinical and translational research (Summative evaluation). Data on CTSI performance will serve to inform ways that the CTSI can be enhanced to improve its mission, redistribute resources more equitably, and which cores are under-utilized or inappropriately used. This systematic measurement of performance will serve as the foundation for necessary changes in CTSI structure and function that will ensure that the CTSI meets its stated goals. The CTSI Evaluation Program is committed to working closely with and providing expertise and data to the National CTSA Evaluation efforts.

### **Process To Address Underutilization, Inappropriate Use, Low Productivity and Other Problems**

To effectively address the results of the internal and external (RAND) evaluations, the CTSI has developed a mechanism that can refocus institute objectives, design and implement new cores and educational and resources initiatives, reallocate funding, and propose and champion University policy changes relevant to its mission. The CTSI evaluations will address, among other issues, use, quality, and productivity of the CTSI and its cores. Identified issues will be reviewed by the CTSI Steering Committee, which will classify them as administrative; education, training, and career development; translational research; clinical research; or translational informatics related. The appropriate CTSI Co-Director or the CTSI PI will then be charged to provide a timely analysis of the issue and a proposed solution. Co-Directors and the PI will be required to solicit feedback from appropriate CTSI Core Directors and others in formulating an assessment and plan. These assessments and proposed solutions will be reviewed by the Steering Committee which, in turn, will make a determination about a CTSI response to the issues raised by the evaluation process.

### **NATIONAL COLLABORATION, SHARING, AND DISSEMINATION PLAN**

The CTSI is fully committed to active collaboration with other CTSA sites at the National level to collectively address impediments to clinical and translational science. The CTSI will work towards adopting and implementing agreed-on best practices, policies, procedures, and other measures to advance collaborative clinical and translational research and to reduce burden on individual investigators at all institutions. The CTSI PI will serve on the National CTSA Consortium Steering Committee and plans to attend scheduled committee meetings. The SVCHS has granted the CTSI PI authority to share and disseminate ideas, experience, and tools, and to act on the institution's behalf to adopt and implement the policies and best practices that are approved by the National CTSA Consortium Steering Committee. CTSI Co-Directors, Core Directors, and members are committed to serving on national CTSA subcommittees to facilitate interactions with other CTSA sites.

**a) Material Transfer Agreements-** Research materials will be disseminated to the nonprofit sector in accordance with the Simple Letter Agreement (SLA) suggested by the NIH as part of its guidelines on sharing of research tools or an agreement of terms no more restrictive than are included in the SLA. The University has prepared form agreements for the transfer of materials, and the responsible office will process such agreements as priority documents. These forms are available on the Office of Research website. Research materials to be transferred to for-profit entities for internal research will be handled in a similar manner.

**b) Data Sharing-** All collaborators will ensure that any data obtained as a part of the CTSI program will be provided to each of the other collaborators and to the general research community by publishing in printed or electronic form as soon as practically possible after the data has been obtained and peer-reviewed. Data may be de-identified as appropriate to ensure compliance with research subject confidentiality requirements. Relevant data will be provided for availability on the appropriate public repository. Initiatives to develop integrative databases will not only allow for data to be available among the collaborators but also in a format that allows for novel uses of the data with other public repositories.

**c) Patent Matters and Licensing of Research Tools.** While it is the general intent of the collaborators to disseminate research resources as provided above, there may be rare circumstances under which the best potential of a particular research resource can be achieved by intellectual property protection and commercial development. All collaborators are fully aware of NIH's intent that research resources become community resources so decisions to file patent applications will be made in light of that intent. Part of the consideration will be the likelihood that the for-profit sector would not develop the research resource without patent protection. In this case, there will be no enforcement of patent rights against any collaborating institution using the patented invention for internal research purposes. One of the vehicles for public dissemination of the research may be licensing to for-profit companies. Nonexclusive licenses of research tools will be favored over exclusive licenses. Any licenses will include diligence milestones to ensure development of the technology. Such agreements will not include product or royalty reach through. All license agreements, exclusive or non-exclusive, retain for the University a transferable right for not for profit research and development purposes.

**d) Software Sharing-** Easy access to software tools and support will be essential to the widespread adoption of translational informatics tools across the CTSA community. The CTSI will use the open source GForge application as the mechanism for distribution, versioning, and support of software for sharing with the CTSA community. GForge provides a complete environment for collaborative software development and sharing, with features including the following: software revision control; task lists, with a plug-in for integration with Microsoft Project; tracking of bug and feature requests, with automated notification via email; discussion groups that can support collaboration among participants at sites worldwide; document management; file release management; A Wiki for collaborative web site authoring; and Custom User Survey forms. GForge was chosen by the NCI as the collaborative development tool for the caBIG program. Prior to that, the University of Pittsburgh caBIG team had developed a GForge site to host the Biomedical Research Integrated Domain Group (BRIDG) project, a collaborative modeling effort that includes the Health Level Seven Regulated Clinical Research Information Management effort and the Clinical Data Interchange Standards Consortium. Software Licensing Principles: All software developed for CTSI should be freely available to biomedical researchers, educators, and institutions in the nonprofit sector (e.g., institutions of higher education, research institutions, and government laboratories). End user license agreements will be developed to be consistent with this mission but will allow for software to be available for commercialization of enhanced or customized versions of the software, or incorporation of the software or pieces of it into other software packages.

## SUMMARY

The University of Pittsburgh is uniquely suited, committed, and obligated to transform its academic culture, environment, and structure to develop clinical and translational science as a distinct discipline in western Pennsylvania. This transformation will lead to fundamental changes in the *institution*, its training of *scientists*, its performance of *research*, and its *health practice* through an unprecedented collaborative effort among the six health sciences schools; UPMC; RAND; CMU; local health professionals, foundations, lay communities, and industry to establish the University of Pittsburgh Clinical and Translational Science Institute (CTSI). The CTSI's primary focus is to build on the University's extensive record of clinical research training, including its existing K30 and Roadmap K12 Clinical Research Training Programs, to develop, nurture, and support a cadre of highly trained clinical and translational scientists. Through "*integration and innovation*," the CTSI will excel in the development of new biomedical knowledge and the translation of that knowledge from the basic and preclinical research settings to individuals, communities, and health practice. These goals will be accomplished by transforming the University of Pittsburgh's extensive activities in basic, translational, and clinical research through novel institutional *integration* of existing programs and the development of *innovative* interdisciplinary research initiatives. The resulting transformation will improve health locally, regionally, and nationally. The CTSI will *transform the institution* by its administration, structure, and governance and will play a substantive role in the training and academic career development of clinical and

translational scientists. The CTSI will also serve as the institutional entity that promotes and supports the conduct of clinical and translational research across all health sciences disciplines. The CTSI will *transform the scientist, research, and health practice* through its ten key Cores that are detailed in this application:

- ***Transformation of the Scientist:*** 1) CTSI Research Education, Training, and Career Development; 2) CTSI Design, Biostatistics, and Clinical Research Ethics; 3) Pilot and Collaborative Translational and Clinical Studies; and 4) Regulatory Knowledge and Support.
- ***Transformation of Research:*** 1) Development of Novel Clinical and Translational Methodologies; 2) CTSI Center for Clinical and Translational Informatics; 3) Participant and Clinical Interactions Resources; and 4) Translational Technologies and Resources.
- ***Transformation of Health Practice:*** 1) Community PARTners (*Partnering to Assist Research and Translation*) Program; and 2) CTSI Catalyst Program

**Table 1. Membership criteria, responsibilities, and benefits in the CTSI.**

<b>Position</b>	<b>Criteria</b>	<b>Responsibilities</b>	<b>Benefits</b>
<b>Member</b>	<ul style="list-style-type: none"> <li>•Established principal and/or co-principal investigator on peer-reviewed clinical and/or translational science grants, or</li> <li>•Record of excellence in teaching in a field of clinical or translational science, and</li> <li>•Peer-reviewed publications in clinical or translational research or education</li> </ul>	<ul style="list-style-type: none"> <li>•Produce scholarly work (e.g., high-quality publications, teaching curriculum)</li> <li>• Participate in CTSI service roles (e.g., serve as representative on Promotions &amp; Tenure Committees)</li> <li>•Acknowledgment of CTSI affiliation in publications, presentations, educational materials</li> <li>•Maintain a regional, national, and/or international reputation, as evidenced by invited presentations</li> <li>•Maintain an active role in CTSI research, educational, administrative, and/or collaborative activities</li> <li>•Serve as CTSI representative in community and at national/ International meetings</li> <li>•Actively participate in CTSI mentoring programs</li> <li>•Serve on CTSI Community Outreach Speakers Bureau</li> </ul>	<ul style="list-style-type: none"> <li>•Eligibility for senior CTSI leadership roles</li> <li>•Academic career development (e.g., academic appointment in Clinical and Translational Science; CTSI role in promotions and tenure processes; OACD support)</li> <li>•Priority and, when available, no cost or discounted access to CTSI cores and services</li> <li>•CTSI translational informatics, educational, and Research Facilitator support</li> <li>•Priority for CTSI novel methodologies and pilot studies funds [that are not specifically focused on junior investigators]</li> <li>•Participation in senior-level and program specific CTSI activities (e.g., retreats, seminars, development of new programs, newsletters)</li> </ul>
<b>Associate Member</b>	<ul style="list-style-type: none"> <li>•Investigator on clinical and/or translational science research projects, or</li> <li>•Teaching in a field of clinical or translational science, and</li> </ul>	<ul style="list-style-type: none"> <li>•Produce scholarly work (e.g., publications, teaching curriculum)</li> <li>•Acknowledgment of CTSI affiliation in publications, presentations, educational materials</li> <li>•Maintain an active role in CTSI research, educational, and/or collaborative activities</li> <li>•Participate in CTSI mentoring programs for high school, undergraduate, and predoctoral students</li> <li>•Serve on CTSI Community Outreach Speakers Bureau</li> </ul>	<ul style="list-style-type: none"> <li>•Academic career development (e.g., appointment in Clinical and Translational Science; CTSI role in promotions and tenure; OACD support)</li> <li>• Access to CTSI resources designed to promote collaborations among institute members</li> <li>•Priority and, when available, no cost or discounted access to CTSI cores and services</li> <li>•CTSI translational informatics, educational, and Research Facilitator support</li> <li>•Priority for CTSI novel methodologies and pilot studies funds [that are not specifically focused on junior investigators]</li> <li>•Participation in senior-level and program specific CTSI activities (e.g., retreats, seminars, development of new programs, newsletters)</li> </ul>
<b>Scholar</b>	<ul style="list-style-type: none"> <li>•Enrolled in CTSI educational programs</li> <li>•Stated commitment to clinical and translational science</li> </ul>	<ul style="list-style-type: none"> <li>•Fulfillment of all requirements of CTSI educational program</li> <li>•Enrollment and active participation in CTSI interdisciplinary mentorship program</li> <li>•Participate in CTSI retreats and seminars</li> </ul>	<ul style="list-style-type: none"> <li>•Designation as a CTSI scholar</li> <li>•Full benefits of CTSI mentorship program</li> <li>•Access to educational core resources (e.g., study design, bioethics, and biostatistical support, biomedical informatics)</li> <li>•Support from Office of Academic Career Development.</li> <li>•Access to CTSI cores and services</li> <li>•Participation in CTSI activities</li> </ul>
<b>Affiliate</b>	<ul style="list-style-type: none"> <li>•Health professional caring for patients who are eligible to participate in research studies, or</li> <li>•Community member committed to the CTSI community-based participatory research program, or</li> <li>•Policy maker actively involved in health care issues</li> </ul>	<ul style="list-style-type: none"> <li>•Active participation in CTSI programs</li> <li>•Enrollment of participants into research studies</li> <li>•Promotion of health awareness, evidence-based practice, and/or benefits associated with participation in clinical and translational research studies</li> <li>•Participation in CTSI Community Outreach Speakers Bureau</li> <li>•Collaboration with CTSI leadership in policymaking processes</li> </ul>	<ul style="list-style-type: none"> <li>•CTSI affiliation/ "branding"</li> <li>•Access to CTSI Community Outreach Speakers Bureau for public health promotional events (e.g., health screenings, seminars)</li> <li>•Priority access to CTSI resources (e.g., educational programs, research support)</li> <li>•Priority in applying for CTSI community pilot studies funding</li> <li>•Participation in CTSI activities</li> </ul>

**Table 2. CTSI Steering Committee Roster**

Name	Position
Steven E. Reis, MD (Chair)	Principal Investigator and Founding Director, CTSI Associate Vice Chancellor for Clinical Research, Health Sciences
Michael Becich, MD, PhD	Co-Director, CTSI
Robert Branch, MD, FRCP	Co-Director, CTSI
Wishwa N. Kapoor, MD	Co-Director, CTSI
Thomas Braun, DMD, PhD	Dean, School of Dental Medicine
Clifford Brubaker, PhD	Dean, School of Health and Rehabilitation Services
Donald Burke, MD	Dean, Graduate School of Public Health (eff. 7/1/06)
Jacqueline Dunbar-Jacob, PhD, RN, FAAN	Dean, School of Nursing
Patricia Kroboth, PhD	Dean, School of Pharmacy
Arthur S. Levine, MD	Senior Vice Chancellor for the Health Sciences, and Dean, School of Medicine
Loren Roth, MD, MPH	Senior Vice President, Quality Care & Chief Medical Officer, University of Pittsburgh Medical Center, and Associate Senior Vice Chancellor, Health Sciences

**Table 3. CTSI Internal Advisory Committee Roster.**

<b>Name</b>	<b>Position</b>	<b>Affiliation</b>
Silva Arslanian, MD (Chair)	Professor of Pediatrics	School of Medicine
David Brienza, PhD	Associate Professor of Rehabilitation Science & Technology	School of Health and Rehabilitation Sciences
Marilyn Brooks, MA	Medical and Science Editor, WTAE	Community
Anthony Delitto, PT, PhD	Professor and Chair, Department of Physical Therapy School of Health and Rehabilitation Sciences	School of Health and Rehabilitation Sciences
Janice Dorman, PhD	Professor of Health Promotion & Development	School of Nursing
Angela Gronenborn, PhD	Professor, School of Medicine; Chair of Structural Biology	School of Medicine
Mary Eliz. Happ, PhD	Associate Professor of Acute/Tertiary Care	School of Nursing
Ronald Herberman, MD	Director, University of Pittsburgh Cancer Institute Associate Vice Chancellor for Cancer Research	School of Medicine
David Kupfer, MD	Thomas Detre Professor & Chairman, Department of Psychiatry Professor of Neuroscience	School of Medicine
Oscar Marroquin, MD	Assistant Professor of Medicine	CRTP Scholar
Roberta Ness, MD, MPH	Professor and Chair, Department of Epidemiology	Graduate School of Public Health
Harold Pincus, MD	Adjunct Professor, Department of Psychiatry	RAND
Samuel Poloyac, PharmD, PhD	Assistant Professor of Pharmaceutical Sciences	School of Pharmacy
James Roberts, MD	Professor and Vice Chair (Research), Obstetrics, Gynecology, and Reproductive Sciences	School of Medicine
Charles Sfeir, DDS, PhD	Assistant Professor	School of Dental Medicine
Jerry Shafran	CEO, Compliance Assurance Corp.	Industry
Francis Solano, Jr, MD, FACP	Medical Director, Inst. For Performance Improvement Clinical Professor of Medicine	UPMC
Jeannette South-Paul, MD	Andrew W. Mathieson Professor and Chair, Department of Family Medicine	School of Medicine
Hilary Tindle, MD, MPH	Assistant Professor of Medicine	K12 Scholar
Raman Venkataramanan, PhD	Professor of Pharmaceutical Sciences	School of Pharmacy
Alexandre Rezende Vieira, PhD	Assistant Professor of Oral Medicine & Pathology	School of Dental Medicine
Sharon Washington	Instructor & Research and Program Coordinator, Pittsburgh Theological Seminary; Associate Pastor, Trinity AME Church	Community
Stephen Wisniewski, PhD	Associate Professor of Epidemiology; Associate Dean for Research	Graduate School of Public Health

**Literature Cited:**

1. Tsugawa B, ed. Section 1: Research Operations: Bridging the Valley of Death. In: The Federal Plan for Meteorological Services and Supporting Research. Fiscal Year 2002; 2001:1-8.
2. Sung NS, Crowley WFJ, Genel M, et al. Central challenges facing the national clinical research enterprise. *JAMA*. 2003;289:1278-1287.
3. Pober JS, Neuhauser CS, Pober JM. Obstacles facing translational research in academic medical centers. *FASEB J*. 2001;15:2303-2313.
4. Israel BA, Schulz AJ, Parker EA, Becker AB. Community-based participatory research: Policy recommendations for promoting a partnership approach in health research. *Education for Health*. 2001;14:182-197.
5. Sawyer RK. *Explaining Creativity. The Science of Human Innovation*. New York: Oxford University Press; 2006.
6. Swazey JP, Fox RC. Remembering the "Golden Years" of patient-oriented clinical research. A collective conversation. *Perspectives in Biology and Medicine*. 2004;47:487-504.
7. Yagi Y, Ahmed I, Gross W, et al. Webcasting pathology department conferences in a geographically distributed medical center. *Hum Pathol*. 2004;35:790-797.



## ***Transformation of Research***

### **Research Education, Training and Career Development**

With the development of the Clinical and Translation Science Award (CTSA), NIH has created a bold initiative to move the disciplines of clinical and translational science (CTS) forward, to remove the barriers between disciplines, to encourage the development of the multidisciplinary and interdisciplinary research necessary to address complex health problems, and to minimize the time it takes to move research from the bench to clinical trials, and ultimately into the community and the bedside. The specific aims of the Education, Training and Career Development Core are 1) to provide early exposure to CTS to increase interests in this discipline; 2) to educate all predoctoral students in the Schools of the Health Sciences (SHS) to the basics of the CTS discipline; 3) to provide opportunities for concentration through certificate (especially for those without access to this training such as basic science PhD students); 4) to offer advanced degrees, including PhDs, for individuals who will become future leaders in CTS; 5) to provide opportunities for faculty to hone their skills relevant to the teaching and conduct of clinical and translational research; and 6) provide education and training opportunities along the entire pipeline of individuals in training to become academicians.

### **B. Background and Significance**

For the CTSI educational component, we convened a working group representing all of the SHS to determine how best to approach such a major initiative to transform the clinical and translational research training and education. This group has met weekly since the release of the CTSA RFA and has been completely invested in finding an approach that works while recognizing the unique needs of each of the Schools. We first determined that the University has a clear strength in the clinical and translational education and a proven commitment to high quality clinical research training as demonstrated through the development of the exceptionally successful Clinical Research Training Program (K30 CRTTP) and the multiple associated innovations as a result as well as the highly coveted Multidisciplinary K12 Clinical Research Scholars Programs (K12 CRSP). The success of these programs resulted in the creation of a home for clinical and translational research training, the SHS-wide Institute for Clinical Research Education (ICRE) directed by Wishwa N. Kapoor, MD, MPH with its dedicated space and staff, which forms the ideal foundation for educational components of the CTSI. To further the success of our educational planning, we also convened several meetings with the Deans of all of the SHS along with the Senior Vice Chancellor for Health Sciences to obtain their input, keep them apprised of our progress in developing a new training schema across the Schools and to garner their support for this plan. The result of these efforts is delineated here: a comprehensive research education, training and career development program that spans all of the SHS, that will provide training in CTS research to individuals at multiple levels from pre-college to graduate and professional levels and will attract those who had not previously considered careers in clinical and translational research to this arena.

**Conceptual framework for CTS as a discipline.** Translation of any new biomedical discovery refers to the process through which that science is used to improve the nation's health. Phase 1 translation, also called "bench-to-bedside" applies scientific discoveries from the laboratory to human health under controlled conditions such as phase I, II, III clinical trials or large scale controlled epidemiologic studies of efficacy in humans. Phase 2 translation is the adoption of effective treatments and scientific discoveries to community-based care under uncontrolled and (often) uncontrollable conditions. We view both phases of translation as highly important. Not only have basic science discoveries to be tested through clinical research in humans but also, once shown to be effective, they have to be incorporated into actual clinical practice in order to lead to improvement of the nation's health rather than just resulting in the acquisition and archiving of new knowledge.

Many barriers exist to both phases of translational research as noted elsewhere in this proposal. The nation's research enterprise currently is very much segregated into separate structures or silos. Lack of communication and effective collaboration often results in lack or delay of translation of important discoveries into effective treatments or integration into practice. In order to effectively translate research at these multiple levels, barriers need to be removed. We envision breaking down barriers and developing actual overlap, consolidation and collaboration so that effective communication and multidisciplinary collaborations are the norm leading to improved translation of scientific discoveries. The CTSI is envisioned to be such a vehicle. Our overall view is that by bringing together many elements of the research enterprise at the University, we will create a new culture and organization that will be much greater than sum of its individual parts. Through this broad integration and transformation, we will develop research and educational programs that will serve as a catalyst for accelerating the conduct of translational research, helping us advance, solidify and promote the discipline of CTS.

CTS as a discipline is currently fragmented and not recognized as a field. The development of CTS as a discipline is vital to the mission of health research for our nation. Key to the overall mission of this discipline—to promote and advance translation of research, beginning from the bench, moving to trials, and ending at the level of community—is transforming the research education endeavor. The educational base includes

quantitative methods (research design, biostatistics, measuring outcomes, etc.), research ethics, advanced statistics and research methods (e.g., phase I, II, III, and community trials), database analysis, qualitative methods, effectiveness research, and others. It will include learning specific areas of the basic sciences and melding the clinical methods with basic research (for example, concentration in immunology for a student interested in drug trials for lupus). Didactic and experiential training in these areas with focus on translation will be important.

Our vision for education in the discipline of CTS is to utilize existing building blocks from many disciplines relevant to this area which will serve as an excellent base. Many new, innovative and novel areas will be developed as the field advances leading to a mature CTS as a discipline. Many of the new educational developments will involve merging and melding various components of education from multiple disciplines (e.g., basic sciences, informatics, epidemiology, computer sciences, psychology) or creating new areas of education that currently do not exist. Because research and education involve multidisciplinary approaches and interactions, new disciplines are likely to emerge. Ultimately the field of CTS has to develop principles and practices that give it an identity. A central element to this identity will be multidisciplinary and interdisciplinary approach to every problem that is encountered in translation. Teamwork and team science will be a core activity in our entire educational endeavor. Through the CTSI, we will build upon our existing broad based education and training incorporating current concepts of the discipline of CTS but always striving to advance the field by developing and teaching new methods so that we can develop this discipline as fully as possible.

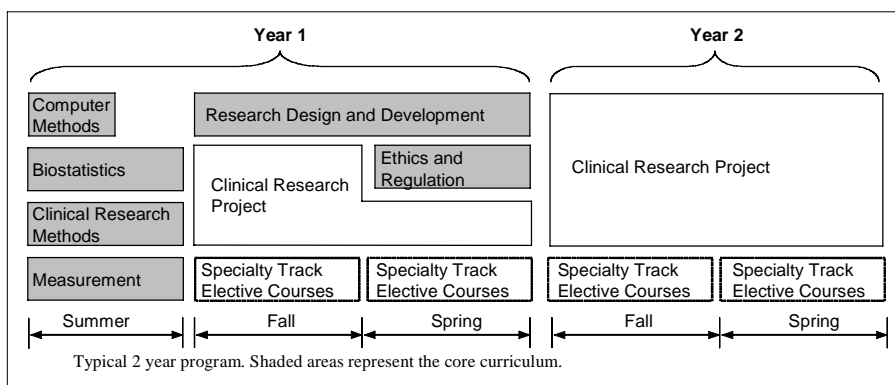
### C. Preliminary Studies

**C.1. Existing Research Training Programs in the SHS.** We have extensive infrastructure in clinical and translational research and education. Our goal, in the CTSI, is not to eliminate or replace current successful training efforts, but to coordinate efforts across the SHS, to enhance existing offerings, and to reduce boundaries between schools and disciplines. In this section, we briefly describe the University's current offerings.

**C.1.1. Institute for Clinical Research Education (ICRE).** At the heart of the clinical research training enterprise is the ICRE, a SHS-wide Institute devoted to the development of high quality clinical researchers. The mission of the ICRE is to offer the highest-caliber training and education in clinical research to all levels of trainees in the SHS and to enhance collaboration among trainees and researchers from multiple disciplines. Established in 2005, under the direction of Dr. Kapoor, the ICRE brings all of our premier clinical research training programs under one organization and into one physical space. The programs, including the K30 CRTP, K12 CRSP and others, are described below. The establishment of ICRE provides University's clear commitment to high quality CTS training. The Institute includes core faculty and mentors from all of the 6 SHS.

The ICRE has dedicated 12,000 sq ft space with smart classrooms, conference rooms (with smart boards), a state-of-the-art computer laboratory, faculty offices, staff space, and 30 cubicles for trainees. This facility allows for effective coordination of programs and mentoring through the close proximity of program staff and faculty. The organizational structure promotes cohesion and opportunities for multidisciplinary collaboration. The Director of ICRE reports to the Senior Vice Chancellor for the Health Sciences.

**C. 1.2. Clinical Research Training Program (CRTP).** The foundation of the clinical research training enterprise in the ICRE is the K30 CRTP, one of the University's major graduate programs, now in its seventh year. This program currently provides a Certificate or Master of Science degree to doctorally-trained clinicians. The figure, below, shows a typical schedule for CRTP MSc degree, designed to take two years, while trainees also have ongoing research. The scheduling of the coursework is done in monthly blocks to make it possible for trainees with some clinical and teaching responsibilities to participate in the training program without major



scheduling conflicts. A large component of both years is the development and completion of the trainee's clinical research project, which is required for the MSc. The thesis requirement can be met by: 1) a standard thesis and defense by the student; 2) an RO1, K-award, or equivalent grant application with trainee as the principal investigator (must be reviewed and approved by an internal scientific review committee); or 3) at least two first-author peer-reviewed publications related to the trainee's research.

**CRTP Core Curriculum** provides basic skills to every clinical investigator regardless of the field of clinic research (shaded areas in figure) including grant writing and ethical and regulatory principles of human research. It begins with an intensive summer program that immerses the trainee in didactic and experiential components followed by the Ethics and Regulation and the Research Design and Development course (grant writing), where the students learn to turn a research question into an NIH-style grant, deal with human subjects issue, and prepare an IRB protocol. The product is a grant application that follows the PHS-398 application format.

**CRTP Specialty Tracks**, distinguished along methodological grounds, allow trainees to concentrate in the type of research they plan for their careers. Taught by faculty from at least 15 disciplines, they include:

*Clinical Trials Research Track.* This track, directed by Robert Branch, MD, Director, GCRC, provides training in the design, conduct, and analysis of clinical trials and relevant principles of pharmacology. To earn an MSc, trainees take required and elective courses and conduct a clinical trials research project. Trainees are encouraged to direct a clinical trial for which they develop the protocol, manage the study, and analyze the results.

*The Effectiveness, Outcomes, and Quality Research Track.* This track, directed by Mark Roberts, MD, MPP, Co-Director CRTP, provides training in health services research. The courses offer advanced skills in analytic methods, effectiveness research, decision sciences, health care quality and cost-effectiveness. Trainees attend CRHC weekly seminars (research in progress, completed research, and health services research methodology).

*Health and Behavior Track.* This track, directed by Paul Pilkonis, PhD, Professor of Psychiatry and Psychology, focuses on bio-behavioral systems, individual processes, interpersonal relationships and behavior and the relationships among them. The MSc trainee completes four required courses and a practicum consisting of a mentored research project, working side by side with the mentor in the development and conduct of research.

*Epidemiology Track.* This track, directed by Roberta Ness, MD, MPH, Chair, Department of Epidemiology, focuses on methodology on the design of experiments and disease prevention. It includes many elective courses from GSPH, and a biweekly research seminar providing an opportunity to develop a grant proposal and have it critiqued by faculty experienced as members of study sections or national review committees.

*Translational Research Track.* This track is directed by Jennifer R. Grandis, MD, Professor of Otolaryngology and Program Leader of the Head and Neck Cancer Program of the University of Pittsburgh Cancer Institute. Trainees in the translational research track have prior or concurrent laboratory experience or plans to partner with a basic science investigator to implement translational research projects in the clinical setting. Trainees participate in the Translational Research Seminar Series that elucidates the basic methods and principles of translational research. Some trainees concentrate on clinical trials, others in health services research or epidemiologic methods and the curriculum is individualized. For example, an individual investigating the effect of genetic polymorphisms in inflammatory cytokines on the risk of organ failure and sepsis-related death will take coursework in the operation of gene chip arrays, basic genetics, and prognostic statistical modeling.

**CRTP Areas of Concentration.** Trainees may elect a concentration in Palliative Care Medicine, Health Disparities, Aging and Chronic Disease or Women's Health. Each area has its coursework relevant to that content area. Table 1 provides a list of 42 new courses developed through CRTP since its inception.

**Table 1. Courses Developed through the Clinical Research Training Program**

Course Name	
Computer Methods in Clinical Research	Best Practices in Clinical Research
Clinical Research Methods	Community and Campus Program and Research Partnerships
Biostatistics: Statistical Approaches in Clinical Research	Research in Health Disparities
Regression and ANOVA	Clinical Trials Practicum
Logistic Regression	Introduction to Pharmacometrics
Survival Analysis	Pharmacogenomics and Risk Disease Models
Applied Nonparametric Statistics	Qualitative Research Methods
Measurement in Clinical Research	Translating Research into Practice
Ethics and Regulation of Clinical Research	Introduction to Patient Oriented Research in Aging
Research Design and Development Seminar	Aging Research in Special Settings
Master's Thesis Research	Special Issues in Clinical Trials in Older Populations
Computer Assisted Epidemiologic Data Analysis	New and Emerging Techniques in Aging Research
Outcomes and Effectiveness Research Methods	Principles and Practices in Palliative Care
Quality Improvement in Health Care	Research Methods in Palliative Care
Quality Improvement Methods and Statistical Process Control	Fundamentals of Bench Research
Quality Improvement Practicum: Tools, Teams, and Design	Translational Research Topics
Cost-effectiveness Analysis	Translational Research Seminar Series
Advanced Methods for Decision and Cost-effectiveness Analysis	Clinical Decision Analysis
Directed Study in Decision and Cost-effectiveness Analysis	Technology Transfer: What Every Scientist Needs to Know
Health Services Research Using Secondary Data: Project	Scientific Management and Leadership
Health Services Research Using Secondary Data: Didactics	Medical Writing and Presentation Skills

**Program progress.** Since 2000, 112 US citizens and permanent resident trainees have been enrolled along with 35 trainees from holdings Visas. Of enrollees, 33 have graduated with Master of Science degrees and 38 remain in the MSc program; 33 have been awarded Certificates in Clinical Research and 15 remain in the

certificate program; many others have taken one or more courses either to strengthen their methodological skills or as part of a K-type career development awards. Of the trainees, approximately 50% are women and 10% underrepresented minorities. We have recruited trainees from more than 30 disciplines.

CRTP graduates have been very successful in applying for grant funding from NIH, AHRQ, private foundations and other sources, and many serve as Principal Investigators. Our graduates have published, on average, 4 papers each with 2.5 being first-authored publications. Finally, all of our graduates are in academic positions except four who have entered into research careers in the pharmaceutical industry and at private hospitals.

The success of the CRTP has led to the development of several innovative clinical research training programs that build upon the coursework of the CRTP. In 2003, we developed the **Clinical Scientist Training Program (CSTP)** for medical students, offering a 5-year joint MD/MSc or MD/Certificate in Clinical Research. Students participate in a 4 year Clinical and Translational Research Seminar series and take the didactic CRTP courses between their third and fourth year of medical school. During 12 full-time months, augmented by 3-8 elective months during the final clinical year, students conduct research. In 2005, we developed the **CSTP for Residents** for Internal Medicine. The didactic program consists of the 2 months of the summer CRTP curriculum, participation in a Longitudinal Clinical Research Seminar throughout three years. Residents do research in a laboratory or clinical research program under the mentorship of an established clinical investigator. **The Clinician Educator Training Program (CETP)** (inception 2002) is designed for fellows and junior faculty who desire leadership roles in academic medical centers and in medical education. Recent enrollees have been from general internal medicine and medical sub-specialties, pediatrics, family medicine, and psychiatry. **The International Clinical Research Training Program (ICRTP)** is designed specifically for non-U.S. based physician-researchers who pursue advanced study in clinical research through a combination of coursework and participation as a member of a clinical research team to return to their country of origin.

**C. 1.3. NIH Roadmap K12 CRSP.** This program (detailed in Section J) prepares scientists from diverse disciplines for independent careers in CTS. It is based in the SHS, the many multidisciplinary research centers at the University, and the University of Pittsburgh Medical Center (UPMC). The scholars engage in multidisciplinary clinical and translational research and pursue education on best practices in clinical research, ethics and regulations, working in teams, and management and leadership skills. Team mentoring is an integral component of the program and is provided by experienced, federally funded senior investigators. This year, CRSP together with the Office of Academic Career Development, created a new course in Scientific Management and Leadership, which is particularly pertinent for the CTSI since, it brings together, for many for the first time, basic scientists and clinical researchers to interact on developing lifelong skills to become leaders.

**C.2. Other Research Training in the SHS.** The SHS provide training in diverse areas such as: biotechnology, trauma and sepsis, clinical research in child psychology, cell and molecular mechanisms of tumor rejection, biomedical informatics, pediatric neurointensive care, pharmacological science, reproductive physiology, psychiatry and psychology, diabetes, chronic disease epidemiology, tissue engineering, and others. Currently, the SHS are home to 51 NIH training (T) grants, 148 NIH career development (K) grants and 39 NIH fellowship (F) grants. All of the SHS have discipline-specific training programs, with many of the courses and curricula directly relevant to CTS research. Samplings of SHS programs relevant to CTSI include the following:

**Table 2. Selected Research Training Opportunities in the SHS** (NIH rank is listed for 2004 and NIH\$ is in millions)

SHS	NIH Rank	# NIH Grants	NIH \$	Examples of Programs Available to CTSI
<b>The School of Medicine</b>	9	700	\$270	<b>Medical Scientist Training Program</b> (offering medical students a PhD at the University of Pittsburgh or CMU); <b>Biomedical Informatics Program</b> (MS, PhD); <b>Interdisciplinary Biomedical Science Training Program</b> (PhD in Biochemistry and Molecular Genetics, Cell Biology and Molecular Physiology, Cellular and Molecular Pathology, Human Genetics, Immunology, Molecular Pharmacology, Molecular Toxicology, Molecular Virology and Microbiology, and Neuroscience); <b>Center for Neuroscience Training Program</b> PhD and MS in lab research and in neuroscience).
<b>Graduate School of Public Health (GSPH)</b>	3	70	\$47	<b>MS/MPH/PhD/DrPH in Epidemiology</b> focused on aging, alcohol, chronic disease, clinical trials, environmental epidemiology, infectious disease, molecular epidemiology, nutrition, psychiatric epidemiology, telecommunications and public health, and women's health; <b>MS/PhD in Biostatistics Program</b> (emphasizing statistical theory and methods); <b>PhD in Environmental and Occupational Health Program</b> (offering training in research in environmental law, management, public policy, risk assessment, and toxicology—reducing the uncertainty in estimating human health risks associated with exposure to potentially harmful agents); <b>PhD in Human Genetics</b> (training in statistical genetics, risk analysis, quantitative genetics, linkage analysis, and other areas related to genetic research); <b>MPH/MS/PhD/DrPH in Infectious Diseases and Microbiology</b> (providing trainees with the research skills necessary to enhance the control of infectious diseases in the human population).
<b>School of Nursing</b>	7	41	\$7	<b>Nursing PhD program</b> (preparing scientists as independent researchers leading interdisciplinary research teams and contribute to the development of nursing science and to the basic and clinical sciences)
<b>School of Health and Rehabilitation</b>	10	8	\$1.2	<b>PhD in Communication Science and Disorders</b> (scientific experience in theories, models, and methods in communication science and disorders to contribute to original research and advance the knowledge base in communication science; <b>Doctoral Program in Rehabilitation Science</b> providing

**ion Science**

training in assistive technology; biomechanical evaluation; evidence-based practice and epidemiology of disability; functioning; information technology; sports injuries; neural basis of sensory and motor function and dysfunction; and psychosocial, cultural, and behavioral aspects of rehabilitation and disability.

**School of Pharmacy** 11 19 \$7

**Clinical Pharmaceutical PhD Scientist Program** (training for independent scientists utilizing contemporary approaches to investigate both the clinical and mechanistic elements of drug therapy issues).

**School of Dental Medicine** 28 10 \$3

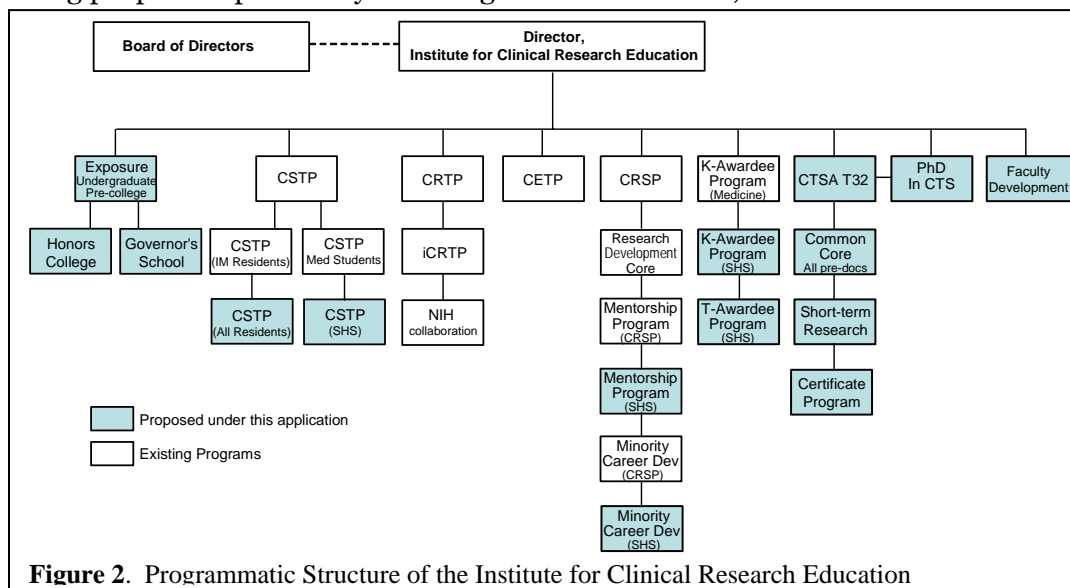
Through the **Oral Health Science Institute** (OHSI) (providing a comprehensive approach to oral health problems including assessment of oral health needs; parental drug abuse and oral health, periodontal clinical and microbiological parameters in diabetes, clinical trials on the prevention of cariogenic infections form mother to child, craniofacial and dental anomalies genetic studies and many other areas.

**C.3. Short-Term Practical Research Opportunities.** In the SHS, there are myriad informal opportunities for students to work full-time with a mentor on a clinical research project for 2-3 months. The SHS are enthusiastic about expanding their curricula in research and to provide additional opportunities for methods training and practical research to interested and motivated students. In table 3, below, we include a brief description of just a few of the existing training opportunities that will be available for participants in the CTSI.

Table 3: Short-Term Training Experiences	Funding Entity	Research Topics
Intramural Training Stipends	Dean, SOM, Children's Hospital Res. Fund	Mentored summer research projects (basic and clinical)
T35 Training Grants	NIH	Neurodevelopmental and Neurodegenerative Disease Program, Short-Term Medical Student Training Program in Renal, Gastrointestinal, Endocrine, and Epithelial Biology, Summer Program for Minority Students
T32 Training Grants	NIH	Cardiovascular Behavioral Medicine Research Training Program; the Clinical Research Training Program in Geriatrics; the Clinical Research Program in Geriatric Psychiatry; the Clinical Research Program in Child and Adolescent Psychiatry; the Digestive Diseases Training Program; and the Research Training in Otolaryngology Program
Magee-Womens Research Institute (MWRI)	MWRI	Summer research experiences to promote interest in biomedical clinical and basic research as a potential career
Nursing Research Courses	NRSA, Hartford Foundation, others	Summer fellowships for interdisciplinary research experiences
Short-Term Dental Student Research Training Program	NIDCR and the Dean's Office	Through summer research scholarship clinical and experimental research training to incoming dental students
Rehabilitation Engineering Research Center Short-Term Training	NDRR	Research through McGowan Institute for Regenerative Medicine, Psychiatry, Physical Medicine and Rehabilitation, Neurological Orthopedic Surgery, Sports Medicine, Neurology, Center for Emergency Medicine, Otolaryngology, and departments of the School of Engineering; and CMU including: Engineering, Computer Science, Design, Psychology and Robotics.
Pharmacy Training	School of Pharmacy	Drug Disposition and Response; Pharmacogenetics, Pharmacogenomics, and Drug Discovery; Neuroendocrine Pharmacology; Drug Delivery and Targeting

**D. Research Design and Methods.**

**D.1. Plans to develop new educational programs in CTS.** We are proposing a breath-taking transformation of our educational programs in the entire spectrum of undergraduate and graduate medical education as well as faculty, community physicians and the public. Figure 2, shows the training program elements currently in place or being developed that will contribute to the educational and career development goals and over all mission of the CTSI. The shaded elements represent the program elements being proposed specifically for this grant. In Section D, we describe new and innovative programs: 1. three



**Figure 2.** Programmatic Structure of the Institute for Clinical Research Education

pathways to doctoral programs in CTS; 2. a common required core education in CTS for all predoctoral students in the SHS; 3. a faculty development program; 4. research certification program for coordinators, research nurses and project managers; 5. a program for junior faculty holding K- and T-type grants; 6. a program for residents and students; 7. programs for undergraduates and 8. pre-college students; and

9. programs for community practitioners and 10. the public. Our newly proposed T32 component is detailed

in section I. We also describe enhancements to existing programs designed for this CTSI, including an expanded mentoring program (section D.8), a minority career development program (section G), and our successful K12 training program (section J). While the proposed transformation is highly ambitious, it is critical to the successful shift of culture in academic research. We are confident we will achieve our goal, given our experience in developing and managing very large and successful programs (such as ICRE), the complete support of the Senior Vice Chancellor for Health Sciences, and the enthusiasm of the SHS.

**D.1.1. Doctoral Programs.** In addition to substantive independent research and rigorous didactic training in CTS, we plan to structure our doctoral program to accelerate the pathway to independence in research using many elements we have implemented in the Roadmap K12. Thus, doctoral students will have experiences in grant writing, scientific writing and presentation, well developed programs on mentoring and career development, learning to work in multidisciplinary research teams, gaining leadership skills and managing a laboratory or a major research program, understanding ethical and regulatory issues in human research, and preparing budgets and financial management. Through these diverse and essential experiences, we will develop investigators who will seamlessly launch CTS research careers directly after their PhD programs. The PhD program is an integral part of the T32 component of this CTSI. Essential elements of our doctoral program in CTS are:

**Didactic coursework.** The conceptual basis of our doctoral program is to develop the career of each student who will evolve into leading multidisciplinary and interdisciplinary clinical and translational researcher. Thus, the didactic training will be developed specifically for each individual. Training will include basic and advanced clinical and translational research methodology, learning about areas relevant to the student's interests but are not part of the core, basic science courses for those bridging bench and clinical research, and courses in other disciplines critical to the student's research endeavor and future concentration. Based on students' career goals, they can pursue coursework in any department or School of the University of Pittsburgh and CMU and specifically in the GSPH, the Biomedical Informatics Training Program, or any of the advanced degree programs in the SHS. The Program Director, the PhD program faculty and the Leadership Council (LC) will work closely with each student to do the following: 1. Review the student's past experiences and competencies; 2. Review the student's career goals and objectives for the core and advanced didactic training; 3. Devise a set of courses, directed readings, or independent study with faculty and mentors or a specialty track area in clinical and translational research that fit the student's needs. We will provide flexibility in advanced course and curriculum selection because of the diversity of the background, training, and future goals of the students.

We will monitor the students' progress as they train and, if necessary, modify the didactic training to meet their needs. We will intervene when problems are identified or there are conflicts. The Program Director and LC will be responsible for making any changes in the didactic training to ensure that career goals are achieved.

**Working in multidisciplinary teams.** This highly interactive seminar series will bring together PhD students, K12 CRSP Scholars, Minority Scholars, their mentors, and senior investigators involved in multidisciplinary research. This series is already in operation as part of the K12 CRSP. Topics include: the development of multidisciplinary research careers, effective approaches to mentoring multidisciplinary trainees, and how disciplines view specific research questions differently and how they may address them in various ways. Using case studies and the students' research, students also explore issues related to investigators' responsibilities in clinical research, such as patient safety, protection of human subjects, compliance with regulatory requirements, and interactions with granting agencies and industry.

Students will be immersed in the highly multidisciplinary and collaborative research and teaching environment provided by the CTSI and the University using many of the institutes and centers as the platform for practical multidisciplinary research training. In cases in which a student requires training in additional disciplines that are not typically represented by an institute or center, we will establish cross-center or cross-institute collaborative efforts. While we view our training programs to be multidisciplinary, we will also promote the development of research careers that are interdisciplinary and that allow students to become future leaders who are engaged in defining new fields of research using interdisciplinary approaches.

**Developing CTS research experiences.** We view research as the fundamental element of the PhD program. The conduct of research will be intertwined with didactic coursework and the doctoral candidates will begin developing research proposals very early in their training as appropriate in their program. We will identify a mentoring team for the students during the first 6 months of the program and will expect that students will begin to develop a proposal for their research. The didactic curriculum to enable this is described below:

**NIH Style Grant Writing.** During the first or second year, students will participate in a 9-month course, Research Design and Development Seminar, which teaches grant writing. Through this rigorous course, students will write a research proposal in the NIH format on PHS-398 forms. Adherence to all federal rules and guidelines regarding clinical research is systematically taught and followed throughout the grant writing process. The grant is developed in small group sessions (with approximately 10 trainees per session), allowing

for extensive interaction among the student and faculty. The students will write an IRB protocol as part of the Ethics and Regulation of Clinical Research Course, which is taught in eight 2-hour sessions during the Research Design and Development Course and tightly integrates the grant proposal writing with IRB protocols and federal regulations. As part of this process, students will prepare a budget for their research projects and a related justification. The CTSI Design, Biostatistics and Ethics (DBE) Core Facility will be used extensively to assist the students in developing their proposals and protocols. The study proposal, protocols, and timetable will be reviewed by a study section consisting of LC members, doctoral program faculty, and additional faculty with expertise in the area of research. All LC members have participated in NIH Study Sections, and the proposal will be reviewed using the criteria and standards developed by NIH. We will use the proposal as the basis of student's research. The grant application will be reviewed and approved by the doctoral committee, after which the students will carry out the study and manage the entire project under guidance of the mentoring teams.

***Project Implementation.*** The students will learn project management through implementation of their research. The practical elements, taught in our existing course on Best Practices in Clinical Research, include: Manual of Operations. The students will develop a manual of operations, delineating details of all study policies and procedures and how they will be implemented, including patient identification, enrollment, obtaining and documenting informed consent, documenting how laboratory procedures and data collection will be handled, follow-up procedures, methods of tracking, quality assurance, and all the remaining details of the study.

Data Collection and Management. The students will work with the mentoring team and DBE Core Facility staff to develop data collection instruments and to design data management and analysis procedures, including procedures for tracking patients, gathering data, and monitoring data quality and integrity.

Personnel Recruitment. The students will recruit any staff needed (e.g., research assistants, data staff) and will develop any contractual agreements needed for data management or laboratory testing and sample storage.

Pilot-Testing. For observational studies, the students will carry out pilot studies of the research protocol to assess the respondent burden, clarity, ease of use, and any other problems with instruments they plan to use. For interventional trials, they will pilot-test randomization and blinding procedures, intervention procedures, data collection plans procedures for handling adverse events, and other facets of the project. For all clinical research projects, they will pilot-test recruitment procedures, patient flow, follow-up procedures, and other elements.

Research Study Implementation. When the mentors and students are satisfied that all elements are in place, the students will carry out the project learning all aspects of a research study. During the implementation phase, students will be responsible for monitoring and maintaining the research costs.

Analysis. Once data have been collected and verified, the students will analyze the data. While the mentors and DBE Core staff will assist and support the students in conducting analyses, we believe that hands-on experience using the statistical skills acquired in the core curriculum is important as reinforcement.

***Dissemination of research findings.*** Using the training from the Scientific Writing and Presentations Course and the experiences of their mentors, the students will submit manuscripts for publication in their research years. They will also present the findings of their research in informal sessions with mentors, LC members, and other doctoral students to refine and hone their presentations. They will subsequently present their findings during the University's Research Day and at national and regional meetings focused on CTS.

***Dissertation.*** To accelerate the pathway to independence, we will use an alternate pathway to dissertation of submitting manuscripts from research for publication to permit the doctoral candidate to write three or more scholarly articles on a related central theme. Two of these articles must be published in peer-reviewed scholarly journals. Each paper becomes a chapter in the dissertation. The dissertation would also consist of background and significance and aims. Conclusions and summary would be written as a traditional dissertation that would integrate the chapters and highlight the major findings from this body of work. This mechanism allows for publication of results in peer reviewed journals where it is more effectively utilized by others.

***Transitioning to an academic career in CTS.*** Because of the long period between grant submission and funding, we will begin addressing future research opportunities early. During the third year and beyond, the Program Director, LC members, and the mentoring team will guide the students in formulating future research initiatives to take the students beyond the PhD Program. We will promote multidisciplinary research grant development that will generally lead to K12, K23 or K25 applications or possibly to R21 or R01 when appropriate. The students will develop a timetable for submissions of grants and work with the mentoring team as well as the DBE Core to design new research projects. They will present ideas and proposals to the LC meetings and obtain feedback. Through a highly interactive process with structured guidelines and timetables, we will assist the students to become competitive for independent funding.

Doctoral candidates will satisfy standard University requirements for preliminary and comprehensive examinations and each will have a dissertation committee consisting of at least 5 members from multiple disciplines.

**Three Pathways to PhD in Clinical and Translational Research:** We have developed three pathways to a PhD in CTS using our model of translational research described above. Two of the pathways consist of transforming currently existing doctoral programs in the SHS to bring new students and investigators into the field of CTS. By reformulating current programs and transforming them into innovative opportunities for translational research, we are creating programs whose sums greatly exceed their individual parts. The third pathway, PhD in Clinical Investigation, is a new doctoral program but it also involves transformation of existing programs. For this PhD, the current CRTP didactic training is augmented by coursework from other SHS, particularly the Graduate School of Public Health (GSPH), to offer a PhD with concentrations in many areas relevant to clinical research such as genetics, behavioral interventions, drug discovery, clinical trials, biomarkers and others. All three pathways will be student-centered and use the principles outlined in section D.1.1. Pathways 1 and 2 PhDs can be started very quickly and we will enroll students in fiscal year 2007. The PhD in Clinical Investigation will be submitted for University approval and will be offered starting fiscal year 2008.

**Pathway 1 Translation: bench to clinical research doctoral program.** We will meld the PhD training programs in basic sciences with CRTP to offer a PhD with a certificate in CTS. All of the SHS provide PhD programs that can be used for this CTSI PhD pathway (shown previously in Table 2). Currently the School of Medicine (SOM) has the largest basic science program with 9 specialized PhDs (See Table 2).

The SOM's basic science PhD includes a common Interdisciplinary Biomedical Science curriculum in the first year (212 PhD students) emphasizing research experience and practical skills. The approach is flexible, and accommodates students whose research interests are still evolving by introducing them to many fields through interdisciplinary courses and laboratory experiences. For students who have a clearly defined research interest, the program offers the opportunity to move quickly into a dissertation project and accelerate their study.

*Foundations of Biomedical Science*, the first course of the Interdisciplinary Biomedical Science Graduate Program, deals with molecular mechanisms of cell and tissue function and an understanding of the experimental evidence supporting these concepts covering the conceptual breadth of biomedical science through integrated presentations from disciplines such as biochemistry, cell biology, molecular genetics and signal transduction. This course is followed by statistics and scientific ethics and then increasingly specialized coursework after the first year when students transfer into one of the degree-granting programs. Students then complete the courses of the selected degree-granting program. There is considerable flexibility in course selection with many electives. We will build upon this flexibility to attract and develop an interest in CTS.

All 9 programs are in their respective departments and led by the Associate Dean for Graduate Studies, Dr. John Horn, who will be part of the Leadership Council of the CTSI PhD program. The melding of the PhD programs in the SOM and the basic science PhDs in the other SHS will be done in the following ways:

**A common core CTS Education for all Predoctoral Students in the SHS.** Central to the CTSI, we will promote the concept that all doctoral students (especially basic science PhDs) need to know how basic discoveries can be translated into clinical research and the implications of their research findings on the health of humans. This will be done through a required common core on CTS described in Section D.1.2. and is part of the T32 component. We will also significantly restructure basic science courses to include a discussion of application to humans through case study method or inviting a CTS investigator to lead one of the sessions.

**Certificate in CTS for basic science PhD.** For those interested in additional training, we will offer a certificate in CTS. The acquisition of a Certificate in CTS has both didactic and research training. The specific requirements are outlined in Section I of this proposal as part of the T32 program. It requires courses in clinical research methods, issues in translational research, ethics and regulation of research, and biostatistics supplemented by elective concentration in many areas offered by the CRTP and the GSPH, including women's health, aging, chronic diseases, HIV, cardiovascular disease, health disparities, diabetes and others. We will have available the entire curriculum of the CRTP and elective courses from the entire SHS for students who wish to get more extensive training in CTS. After fulfilling the core requirements of the basic science PhD, CRTP or GSPH courses will be then added as part of their elective and become an area of concentration. A curriculum will be jointly developed between the CTSI and the doctoral students in conjunction with their mentors/advisors addressing the interest and needs of the student. The didactic training will be complemented by a multidisciplinary research experience involving basic and clinical researchers. The doctoral committee and mentors will include faculty from clinical and basic research disciplines. We will require that the research dissertation be in translational sciences involving laboratories of clinical and translational investigators.

**Pathway 2 Translation: Translating Research into Practice Doctoral Program (TRIP PhD).** The barriers to incorporating research into practice are many including provider knowledge and behavior, lack of team approaches to care, lack of electronic medical system (EHR), inability to provide effective patient



education and others. There is an extensive literature on methods of provider behavior change, reminders, feedback, use of alerts, Electronic Medical Record (EHR), pharmacy interventions, team approaches to care, models of chronic disease management, quality improvement methods and others. This area of research needs further development not only in new methodology but also how it can be applied to health systems and practices. Especially important is the use of informatics, information technology, the internet, EMR, hand held devices, smart cards and many other cutting edge technologies. Additionally office, hospital and practice redesign are very important in our ability to transform the practice of medicine. Opportunities in this area of CTS are extensive, and effective interventions in TRIP will have a major impact on the health of the nation. Additionally, the TRIP area of science will also be important for many of the basic discoveries that will need to be eventually translated into practice. We will coalesce strong programs in Pittsburgh to develop an innovative doctoral program. Beyond ICRE, previously described, two other major programs will be brought together for TRIP PhD.

**The Biomedical Informatics PhD Program** prepares individuals for research and development careers on the application of technology to health care, basic biological and clinical research, and the education of health professionals. The program is for individuals seeking formal training in informational and computational methods, or others who may be scientifically trained and seeking to prepare themselves for careers emphasizing biomedical applications of information technology. The program currently has 40 students and accommodates diverse backgrounds and aspirations of its students. Active participation in research is a key element of the training and opportunities are available for both applied and theoretical research. We offer both master's and doctoral degrees in Biomedical Informatics, as well as non-degree Postdoctoral Fellowships. Currently concentrations of study can be obtained in the areas of biomedical informatics, dental informatics, health services research (with CRTP), and public health surveillance. Funding for the program is primarily provided by the National Library of Medicine. The training program draws on faculty throughout the University of Pittsburgh with 30 core faculty and over 50 affiliated faculty, who span a total of 6 schools and 12 departments.

**The Human Computer Interaction Institute (HCII)** is an interdisciplinary program at Carnegie Mellon University (CMU), Pittsburgh, dedicated to research and education on computer technology in support of human activity. Although the HCII is headquartered in the School of Computer Science, faculty and students represent a broad spectrum of CMU including the College of Humanities and Social Sciences, the Tepper School of Business, College of Fine Arts, Carnegie Institute of Technology, and Software Engineering Institute. HCII research and educational programs span a full cycle of knowledge creation, including research on how people work, play, and communicate within groups, organizations, and social structures. It includes the design, creation, and evaluation of technologies to support human and social activities. The HCII has a record of evaluating and monitoring the immediate and longer-term usability and social aspects of new technologies and tools.

*Candidate for TRIP PhD.* This program will bring diverse students together including doctoral students from CMU, Biomedical Informatics, CRTP, predoctoral students from the SHS as well as fellows and junior faculty in the School of Medicine. Medical students may be accepted into this program as MD/PhD candidates.

*Program Structure.* CMU HCII will add a track in **Clinical and Translational Sciences** into its PhD program and, thus, the degree will be granted by CMU. The Biomedical Informatics PhD program will add a track, Translational Research, and degree will be granted by the University of Pittsburgh. Biomedical Informatics currently has a MS degree in Health Services Research (jointly offered with CRTP) which will be transformed to offer this PhD. A common curriculum committee for TRIP PhD will be formed with equal representation from all three programs. All dissertation committees will represent faculty of the three programs and will jointly approve the dissertation. The Leadership Council (LC) will consist of the core faculty of the three programs and will jointly meet to approve the entire training program for each student. The LC will also meet regularly to monitor progress and address problems.

*Curriculum.* There are 4 cores for this program and students select courses from 3 of the 4 cores. Students selecting the TRIP will take the required core for the Certificate Program in CTS as described above and in Section I below. We will also enhance a current course, BIOINF 2013: Clinical and Translational Environments in Biomedical Informatics (3 credits), which will be jointly taught by CRTP, biomedical informatics and CMU faculty. Students will be placed as observers in clinical environments relevant to clinical and translational research at UPMC. Specific class assignments and questions associated with these observations will encourage active learning about the environments in which clinical and translational research are currently performed, how that research is currently done, and how it might be advanced. This course will introduce and enhance knowledge about clinical practice and its impact on TRIP. A current CRTP course on Translating Research into Practice will be enhanced to include informatics, EMR, internet and technology methods used to transform practice.

The other three cores will vary depending on the students entering the PhD at CMU or the Biomedical Informatics Program. To accommodate diverse backgrounds of students in HCII PhD, that program is structured around three areas of specialization: behavioral sciences (encompassing, for example, social science, cognitive science, or psychology backgrounds), computer science, and design. We will add Clinical and Translational Sciences as another area of specialization drawing from extensive didactic offering of the CRTP, GSPH, and SHS. The didactic programs are created individually, but must be approved in advance by both the student's advisor and a joint curriculum committee. All programs of study will include the HCII course on Process and Theory; 4 graduate level courses in an area of specialization; 2 graduate level courses in a second area; and 1 graduate level course in a third area. Each program of study also includes at least one graduate level studio design course. Students may take biomedical informatics courses depending on their career goals and interests.

Biomedical Informatics PhD students will take the biomedical informatics methods core which includes courses in problem-oriented programming, data structures and algorithms, information technology, methods and principles of user-centered design, technology transfer, and others. They may take electives from the spectrum of CRTP courses as well as HCII courses as meeting their career goals. CRTP students generally will have completed a MSc degree in clinical research. They will take HCII core courses if they plan to get a degree from CMU. They would apply for this degree to CMU with the support of ICRE. Similarly they may enroll in the Biomedical Informatics PhD program and will take these courses as deemed appropriate for their career goals.

**Dissertation.** In general students will work in the laboratory or research programs of established investigators who could be from CMU, Biomedical Informatics and or other programs. We have a very robust health system with research and development initiatives with IBM, Intel and other major computer companies. There is extensive effort at UPMC on EMR development and use, use of the Internet and other technologies.

Dissertation projects may be proposed and supported by the UPMC but the central element of the dissertation would require transformation of care for the purpose of translation into practice.

**Pathway 3. Doctoral Program in Clinical Investigation.** This program will build upon the strengths of the School of Medicine, the ICRE, the GSPH programs, the PhD in the School of Pharmacy, PhD programs of the School of the Health and Rehabilitation Sciences, and the doctoral program in the School of Nursing. Students from diverse disciplines may enroll in this multidisciplinary PhD program. The courses for the didactic components will come from multiple disciplines and trainees from diverse disciplines will interact with each other extensively. Mentoring and advising will also be by a multidisciplinary team. We view the role of CTSI Education Core is in carefully crafting the didactic components after extensive discussions with the candidate and customizing a program that meets the career needs of the trainee. The CTSI will also lead the effort in developing the multidisciplinary and team research that is a central element of this PhD program. We have designed four cores: Analytic, Clinical and Laboratory Methods, Translational Methods, and Practice of Research Cores. Additionally, there will be content area electives and a doctoral dissertation. We will utilize the extensive offerings of the SHS, consisting of more than 300 credits. The didactic courses will be chosen to best suit the career goals of the student. There are no barriers to taking courses across schools and we have extensive experience in offering courses from multiple schools in the CRTP. The design of the Cores is consistent with the principles outlined in our overview above. We will bring together students from multiple disciplines to the same classrooms as well as teachers from multiple disciplines to teach together. We will also require that students take courses at least in two different SHS so as to increase the understanding of other disciplines.

The *Analytic Core* will provide methodological training needed for CTS investigator and includes 7 credits of required courses, including clinical research methods and biostatistics. They will then choose additional courses from the CRTP or courses offered in GSPH or other SHS to develop depth of methodological expertise.

The *Basic and Laboratory Methods Core* will include courses available in the SOM and other SHS for students interested in the Basic and Laboratory Methods Core. For example, the CRTP offers a course on the Fundamentals of Bench Research; the SOM offers courses on Foundations of Biomedical Science. Students will select courses depending on their career development goals and basic research interests.

For *Translational Methods Core*, students may select courses from the Translational Research Track of CRTP (e.g., technology transfer, translational research topics, translating research into practice and others). Courses from other schools may include, for example, biomarkers and molecular epidemiology, Pharmacogenomics, systems approach to inflammation, and others depending on the student's particular needs and interests.

The *Practice of Research Core* takes advantage of the many research methods and related courses of the CRTP, including the Research Design and Development Course (grant writing), Best Practices in Clinical Research, Ethics and Regulation, Scientific Management and Leadership and Seminars in Multidisciplinary Research. Other potential courses are included in Table 1 and may include: clinical trials, medical writing, and others.

**Research.** A major component of PhD program will be mentored research. The research is modeled after our highly multidisciplinary and successful K12 Roadmap program. In this program, each Scholar has a team of

mentors who are from at least two entirely different disciplines. We promote team mentoring and require that team mentoring occur regularly and the entire team meets weekly. As in the K12 CRSP, the research will generally be based in a CTSI collaborative research center or institute, which are the hubs of multidisciplinary research. In general, the PhD program will be completed in 4-5 years. The coursework will be completed within the first 2-3 years. Students will begin planning their research during years 1-2, receive approval of their dissertation at the end of year 2 and begin research at that time while completing the coursework.

**Areas of Concentration.** Fundamentally, doctoral programs are judged on three dimensions: quality, depth, and breadth. The Cores for the PhD in Clinical Investigation provide a high quality fundamental methodological training. To provide the depth and breadth, we have also identified areas of concentration such as: clinical trials, translation of genetics into clinical research, decision sciences and modeling, computational biology, community-based research, health disparities, health economics, women's health, palliative care, risk communication and others. All of these areas of concentration can be fulfilled through the conduct of coursework through the GSPH or CRTP, making the concentrations an immediate reality.

**D.1.2. A Common Core CTS Education for all Predoctoral Students in the SHS.** As part of the T32 component (described in Section I), we will develop a two credit, team-taught, seminar series that will be required of all doctoral students in the SHS titled *Introduction to Health Science Research: From Bench to Bedside to Community*. The goals include: 1) education about the complex context in which health science research occurs by examining critical agenda setting documents about future research (*Healthy People 2010*, *The CDC Research Agenda*, the NIH Roadmap, IOM reports including *The Future of the Public's Health in the 21<sup>st</sup> Century*, the Community Guide to Preventive Health Services, and *Clinical Research Roundtable Workshop on The Role of Providers in the Clinical Research Enterprise*); 2) expand the exposure of each discipline to the benefits of multidisciplinary research through case-based examples of successful multidisciplinary research developed within and outside the University; 3) foster an understanding of the need for translation of scientific research from bench to bedside to population; and 4) provide an experience in multidisciplinary collaboration by requiring participation of multiple disciplines in each seminar and incorporating a multidisciplinary team taught course format. This core course will also enable students to appreciate the iterative nature of scientific inquiry that allows for research questions to emerge from clinical and population-based practice.

This seminar represents a substantial commitment from all of the SHS and all SHS have demonstrated commitment to its development. The seminar will be required of all doctoral students in any discipline, will be taught in sections that, by design, will contain students from virtually all doctoral programs and each section will be co-facilitated by faculty members from at least two disciplines. Working in a multidisciplinary group, the students will engage in a final project that proposes the translation of research findings to one of several areas: clinical practice, population interventions, or policy. For example, a group consisting of students from microbiology, pharmacy, behavioral and community health sciences, fellows from infectious diseases, and the CRTP may develop the process for translation of a promising avian influenza vaccine to clinical trials to policy implications. In doing this, they will consider the larger agenda setting frameworks that influence health research today, including Healthy People 2010, the NIH Roadmap, among others.

**D.1.3. Faculty Development Program (FDP).** The objective of FDP is to provide multi-tiered, comprehensive faculty training in CTS, fostering a cultural shift in research focus among the basic and clinical research faculty participants. The program will provide the requisite skills in CTS and develop collaborations to conduct multidisciplinary research. In its simplest form, the program will provide a forum for interaction of clinical and basic faculty with similar research interests to build multidisciplinary collaborations. More advanced training experiences will provide faculty with bench and/or clinical research skills to catalyze their research interests. These experiences coupled with an active mentoring program are expected to create a cultural shift by the faculty that will permeate throughout the SHS PhD training programs. We will use the Office of Academic Career Development, Health Sciences under Dr. Lakoski to develop and lead this program. Tiers include:

**Level 1: Faculty Retreat on Clinical and Translational Research.** We will develop a two and a half-day faculty retreat open to all faculty of the SHS focusing on concepts of translational research, collaborations, opportunities, funding mechanisms, and in-depth sessions on topics in CTS disciplines (e.g., biomarkers, translating research into practice). The retreat will be coordinated with the annual CTSI "Synergies in Health Research Day," which will focus on clinical and translational research. Furthermore, two Translational Research Awards will be made at the meeting, one to "Outstanding New Investigator Award in CTS" and the second for "Scientific Achievement Award in CTS." Collectively, the goal of the Level 1 program is to provide training, incentives and programmatic forums to promote clinical and translational research in the SHS. This program will utilize current multidisciplinary research programs to broaden the horizons of both basic and clinical faculty about the opportunities for cross-disciplinary collaboration in CTS.

**Level 2: Mentorship and Certificate Course Opportunities.** Faculty with interests in developing clinical and translational research skills will have the opportunity to apply for CTSI Training Award. Faculty selected, will take courses (90% of the tuition is covered by faculty benefits) and will have a designated CTSI advisor, a senior faculty with established success in clinical and translational research. Together the awarded faculty and the advisor will draft a development plan that includes regularly scheduled progress meetings, faculty registration in the courses offered as part of the Graduate Certificate in CTS, and linkage to multidisciplinary teams with similar research interests among the SHS faculty. The program will be one year in duration with opportunities for the faculty to extend the training for completion of the graduate certificate.

**Level 3: Mini-Sabbatical in Clinical and Translational Research.** Select faculty, with the support of their departments, will participate in a mini-sabbatical, which will allow them to conduct translational research in either their own or their mentors' laboratory or in another setting either within or outside the University. Our PhD partner, CMU, has enthusiastically offered to host mini-sabbatical experiences in medical robotics, medical devices, computational biology, computational neuroscience and other fields as part of this program. The goal will be to provide specific skills (coursework, directed reading and collaboration with a CTSI faculty) to advance their research interests in CTS. We expect the faculty will gain the skills and networking through the mini-sabbatical to generate preliminary data for CTS research proposals to the NIH.

**D.1.4. Program for Coordinators, Research Nurses, Project Managers, and Investigators.** We will develop a required certification program for research coordinators, research nurses, project managers, and investigators who conduct CTS research in the SHS. While we understand that this program is ambitious, we believe that it is extremely important to transforming the research culture while ensuring high quality research as well as institutional accountability for the conduct of research. This will ensure a cadre of trained personnel who are qualified in the conduct of clinical and translational research. To ensure integration with existing information technology resources and promote the development of innovative IT solutions to educational barriers, the CTSI Center for Clinical and Translational Informatics (CCTI) will be integral to program development. To maximize success, development of the program will adhere to adult learning principles and will utilize a systems-based approach. This program will be guided by the ICRE Board of Directors (see Section D.3) and the leadership of the CTSI Education.

This program will build upon the concepts introduced in the Research and Practice Fundamentals Training (described in Section F) and the curriculum will be based on that utilized in the highly successful Research Coordinator Orientation and Pitt Research Network. The training program will consist of a mandatory core component that will provide trainees with a standardized set of skills and knowledge that are fundamental to all types of research. Core topics will include: Research Regulations and Guidelines, Research Ethics, Research Integrity, Good Clinical Practice, Standard Operating Procedures, IRB submissions, Screening, Recruitment and Retention, Informed Consent, Safety Issues, Fiscal Issues and Study Documentation. Additional elective topics offered will include: Data Management, Responsible Literature Searching, Advanced Budgeting Concepts, NIH Reports, Drug and Device Studies, Managing a Coordinating Center, Conducting International Research, Issues in Behavioral Research, Monitoring and Audits, and others. Trainees will be required to complete one continuing education elective per year to maintain certification. This approach will promote learning by providing an opportunity to self-select into a course that is meaningful and relevant to the participant. This program will employ a combination hands-on and internet based approaches through existing and new seminars and workshops to accommodate the busy schedules of research personnel while ensuring a comprehensive education with required web-based proficiency tests for certification.

**D.1.5. Program for Research Career (K) and Research Trainee (T) Grantees.** A significant portion of K awardees do not go on to receive NIH R- grants for future research. Career transitions from K to independence will be a major area of focus for the CTSI Education. To increase the success of transition from individual K in the Department of Medicine (DOM), we devised a program that provides support and guidance for K awardees and a collaborative environment of peers and advisors to assist individuals in their career paths. As part of the CTSI, we propose to broaden the program to include all K and T awardees in the SHS. The program we envision is akin to the DOM's program and is based, in part, on the program we have developed for the K12 CRSP. Through this program, all K and T awardees, including the K12 BIRCWH Scholars, will be provided with an advisor as well as the mentors with whom they are currently working. The advisor will be a senior investigator and, when possible, will be a recipient of a K24 (mid-career mentoring) award. The advisor will monitor the progress of the K and T awardees to ensure that the individual remains on track with respect to training, that the mentor-mentee relationship is successful, and that the research is making excellent progress. All K and T awardees will be assigned to small groups (less than 10) under the leadership of the advisor, and they will meet monthly to discuss their progress and to troubleshoot problems. A central aim will be to help junior faculty and trainees to develop and submit new grant proposals to transition from career development awards to become independent investigators. These meetings will provide the opportunity for networking with other junior researchers, collaborating with individuals from other disciplines, sharing ideas

and issues, and problem-solving. Periodically, the entire group of K and T awardees will gather to meet each other and share experiences, participate in workshops, and discuss issues critical to their development as CTS investigators. Throughout the year, as new K and T grants are awarded, these investigators will join the program, forming a network of junior investigators. This program will be led by Susan Greenspan, MD, who currently holds a K24 mentoring award, and Stephanie Studenski, MD, who leads several T32 initiatives. The Director of CTSI Education will work closely with them to make this program a success.

**D.1.6. CTS Education for Residents and Students.** We currently have a CTSP for Internal Medicine residents—the purpose of which is to increase the pool of physicians to pursue careers in clinical research. We offer intensive didactic training through one summer when we protect 100% of the time of the resident for CTS research training and starting a research project. We also provide monthly seminars, bringing senior clinical and translational researchers to introduce clinical research concepts and methods as well careers. Research is planned very early and conducted under one or more mentors over the entire period of the residency. This program is very popular and we currently enroll 10 residents per year. Under the CTSI, this program will be expanded and offered to residents from all the specialties. The structure of the program will be as follows:

1. Short term 2-3 month research experiences. Residents choosing this will have the opportunity to attend the longitudinal seminars. ICRE faculty will identify mentors to carry out research. The culture of research in residency is that beyond the protected time provided by the program (which is largely regulated by the ACGME and differs from specialty to specialty), they often work during their clinical rotations (such as elective rotations, ambulatory experiences) on research projects. Research or a scholarly project is a central component of every residency and we will utilize this to help guide the residents into meaningful research experiences in CTS.

2. Certificate in CTS. This will be possible in specialties where protected time is allowed by the Residency Review Committees of the ACGME (a minimum of 6 months). A major part of the didactic program for a certificate through K30 CRTP can be completed in the 2 summer months. ICRE will coordinate the research component to integrate residents into a laboratory or program under the mentorship of an established investigator.

3. MSc or PhD degrees in CTS. For residents interested in taking 1-5 years out of residency, we will make all of the didactic and career development opportunities outlined under the PhD and MSc program available to them. Funding will largely come from the laboratories and research programs, while training components will be from the ICRE, which will support and coordinate their career development and research program.

We also have CSTP for Medical Students described in C1.2. This program will be available to students from the SHS. Additionally, a predoctoral T32 program is proposed (section I) for students from all of the SHS.

**D.1.7. CTSI Program for Undergraduates.** To promote recruitment of the most talented undergraduates into CTS careers, we will provide experiences in clinical and translational research within the University's Honor's College (UHC). The UHC was established in 1986 to meet the special academic needs of its most capable and motivated undergraduates, providing opportunity, incentives, and recognition for high academic attainment. University-wide in scope, the UHC fuses the scholarly advantages of a major research university with the individualized attention, rigor, and educational commitment of the academically demanding small college. The CTSI Undergraduate Program will expose the UHC students to clinical and translational research and provide an opportunity for exploration of related career paths during the formative years of education. We will leverage existing programs within the UHC; specifically, the Friday Afternoon Lectures and the Undergraduate Research Scholarships and Fellowships programs. The goal of Friday Afternoon Lectures is to facilitate understanding, promote discussion, and encourage continued exploration of diverse topics. A member of the ICRE faculty will participate in this program each semester by delivering lectures on CTS projects.

We will select talented students for 'shadowing' experiences, matching them with clinical researchers who they will follow for a duration (usually two weeks) to observe their research activities, participate in research team meetings, observe mentoring interactions, and develop an excitement about CTS research. The UHC makes a special effort to prepare students for prestigious merit-based national and international scholarships. We will leverage these resources for short-term experiential CTS research projects. We will maintain contact with promising undergraduates with interest in the health sciences through newsletters and mailing lists and will invite them to special events throughout their undergraduate years to increase their interest in CTS careers.

**D.1.8. CTS Education for Pre-College Students.** The Pennsylvania Governor's School (PGS) program, sponsored by the Commonwealth of Pennsylvania, provides promising junior high school students a five-week summer residential scholarship to complete a rigorous academic program at a University. There are 8 PGSs; each one has a specific focus and is affiliated with a University with excellence in the focus area. The admission process is highly selective, with the PGS for Health Care accepting 110 students per year at the University of Pittsburgh. PGS introduces students to the world of health care, with exposure to areas such as public health, primary care, prevention, and specialty practice areas. The PGS for the Sciences is located at CMU, exposing

them to disciplines such as biology, chemistry, physics, and biomedical informatics. We will use PGS to promote the recruitment of new investigators in CTS careers by exposing talented students to this career choice. In collaboration with the PGS, the CTSI Education Core will develop and provide three types of participatory activities designed to increase engagement by providing a contextual learning experience:

1. Interactive lectures wherein clinical and basic scientists engaged in a collaborative project discuss their research, with an emphasis on real-life applications for all students at both PGS programs (N=210).
2. Site visits to the laboratory/clinical area where the CTS research is being conducted for self-select interested students. The PGS anticipates that approximately 20 students per program will participate (n=40).
3. A shadowing experience with CTS researchers will be arranged for 5 students.

After the program, we will maintain contact with the students through bimonthly newsletters and mailing lists and will invite students to the University's Science Day. A letter of support from the PGS is attached.

**D.1.9. A Program for Community Practitioners.** This program will develop educational initiatives targeting multidisciplinary community-based practitioners to 1) foster an understanding of CTS research, 2) facilitate engagement in the CTS research, and 3) promote evidence-based practice via the integration of research findings into clinical care. We will work with the Community PARTners Program (described elsewhere).

**D.1.10. A Program for the Public.** The projects designed for the public are described in the CTSI Community PARTners Program. We are collaborating with this core to develop educational programs.

**D. 2. Novel concepts, methodologies, and approaches that integrate the education, training and career development environment.** The Educational and Career Development components of the CTSI will transform the traditional clinical research endeavor through cross-school and cross-discipline collaboration in training and team-building. We are developing a new way of training researchers that will reduce or eliminate barriers between basic and clinical research, among schools, and across disciplines to accelerate the translation of discoveries into clinical research and practice. Innovative approaches include:

**The inclusion of all of the SHS in advancing the discipline of CTS.** Participation in a common core on CTS for *every predoctoral student* in the SHS will integrate the educational environment and help build multidisciplinary collaboration.

**The development of three pathways to a PhD.** Our PhD pathways merge multiple disciplines to create innovative training and career development options. They bring together successful groups (CMU computer sciences, biomedical informatics and CRTP) to offer unique and innovative approaches to doctoral training in CTS. Additionally, flexible training programs for the PhD basic scientists to develop CTS careers integrates the education and training environment and encourages basic scientists to focus on translation.

**The development of an advising and mentoring program for all individual K and T awardees in the SHS.** This program will enable CTSI to provide the support and monitoring for greater success of the K and T awardees, improving successful transition to independence and accelerating career transitions.

**A program for certifying coordinators, research nurses, and managers.** This innovative program will ensure that all staff and faculty involved in clinical research will have received training and passed certification requirements ensuring that research conducted is of the highest quality, effectively protects the rights of human subjects, is ethically conducted, and adheres to all federal regulations.

**The development and expansion of a program to promote minority careers.** Through this novel program, we will provide training and support for minority individuals early in their careers to allow them to acquire skills and competencies for a successful research career upon completion of training.

**Coordinating existing programs with new programs.** We use innovative methods to build upon existing successful programs to create educational opportunities for the pipeline in CTS research such as using the University's Honor College to introduce undergraduates to CTS and new programs and experiences in clinical research for pre-college students to be implemented through the existing Governor's Schools.

**Novel approaches to the career development for K12, K30, T32, PhD, or other programs.** The unique elements with a major impact on the training and career development include: 1) student-centered didactic programs (individualized courses and curricula) to accelerate career development to independence; 2) grant writing experience early in the students' training jump-start their investigative careers; 3) training in working in multidisciplinary teams; 4) training in leadership and project management skills; 5) training for mentors and mentees; 6) training existing faculty to improve CTS teaching and to facilitate transition into CTS research careers; and 7) individualized attention to interventions on transitioning careers.

**A continuum of training.** Our comprehensive approach to education (starting at pre-college and continuing through the spectrum of predoctoral and postdoctoral training to training faculty to educating public and community physicians) will help develop pathways (e.g., undergraduate students may get

hooked onto CTS, pursue an MD (or other professional degree)/MSc or PhD in CTS, then become CTS researchers as they continue their careers). This will allow us to integrate and interdigitate career pathways.

**D. 3. How the K and T components will be configured, operated and governed.** The CTSI Training and Career Development core will be directed by Dr. Kapoor, Falk Professor of Medicine and Professor of Health Policy and Management; the Director of the ICRE; the Director of the Center for Research on Health Care (CRHC); the Chief of the Division of General Internal Medicine; and Director of the K30 CRTP and the K12 CRSP. He serves as Vice Chair for Education in the Department of Medicine. He is a member of the American Society for Clinical Investigation and the Association of American Physicians, and he previously served as President of the Society of General Internal Medicine and Chairman of the Federated Council for Internal Medicine. Dr. Kapoor is an internationally recognized expert in clinical research and clinical research education, focusing his efforts on clinical epidemiology and health services, with studies on common medical problems such as syncope and community-acquired pneumonia. Dr. Kapoor is a leader in clinical research education, having developed several fellowship training programs and mentoring programs as well as major NIH training initiatives, including the K30 CRTP and the K12 CRSP.

Dr. Kapoor will be responsible for all aspects of the Education, Training and Career Development for the CTSI. He will lead the implementation efforts and will develop the evaluation component working closely with the entire CTSI evaluation team (using our experience with K12 as a guide). The governance will be configured as:

1) A Board of Directors of ICRE will be appointed by the six Deans of the SHS and will include their representatives and 1-2 senior members of the advisory committees of K12, K30, T32, Mentoring, and PhD programs. Additionally, 1 representative from each of the CTSI cores will become part of the Board. The Board will oversee all ICRE functions, CTSI training, education and career development programs, participate in retreats, advise on the evaluation plan and help coordinate all the elements of the CTSI Education with other components.

2) Core and Affiliate Faculty appointments in the ICRE. The Board will develop and implement appointment criteria. All of the mentors will have to be approved as core or affiliate faculty by the Board and participate in mentor training. ICRE faculty will be those conducting substantive CTS Research or who are the major teachers of the CTS discipline. Developing core faculty designation help bring a community of CTS investigators together for joint functions, training, career development, and new research methodology development. Affiliate faculty would be those who have an interest in CTS but currently may not be involved in CTS Research (e.g., basic scientists with future interest in translation). This mechanism has allowed us, for example, to develop a community of health services researchers in the CRHC and may bring together 300-500 or more faculty interested in CTS. ICRE will provide incentives for faculty to become Core and Affiliate members by: access to seminars, conferences, assistance in developing K12 and other K grant applications for junior faculty, ease of access to CRTP, ease in identification of mentors, and recognition of faculty appointment for tenure and promotion.

3) Advisory Committees (AC) and Leadership Councils (LC). Each of the major programs will have an AC (active K12 and K30 AC already exist) and LCs are proposed for the PhD program and the Common Core. The AC will guide the overall direction, focus, and components of each program. Responsibilities include a) reviewing applications and selecting Scholars, students or trainees; b) establishing, reviewing, and monitoring the curriculum and recommending changes if needed; c) developing and approving individually-tailored education, career development plans, and research projects for Scholars, students or trainees; d) providing monitoring and evaluation of each Scholar, students or trainee's progress with recommendations for modification or, if necessary, termination when there is inadequate progress; and e) reviewing compliance with criteria for awarding a certificate, MSc and PhD Degrees. The ACs will have representation of senior investigators from all of the SHS. The current Multidisciplinary Advisory Committee (MAC), representing all of the SHS, for the K12 and the AC for the K30 will continue (the latter will broaden its representation to include all SHS). The coordination of the programs will be done through the ICRE Board and presented to the CTSI Steering Committee.

All the AC and LC will meet regularly (at least monthly). An Executive Committee of the ICRE will meet weekly and will consist of the leadership of all of the programs in CTSI Education Core. The executive committee will be responsible for the day-to-day management of the entire educational, training, and career development effort of the CTSI. The table below shows the organizational and governance structure of CTSI Education Core:

Function	Name	Discipline
Director:	Wishwa N. Kapoor, MD, MPH	Internal Medicine
Mentoring, Career Dev Director:	Joan Lakoski, PhD	Pharmacology
Asst. Dir. for Mentoring:	Megan Cunnane, MD	Internal Medicine
Asst. Dir. for Career Develop:	Beth Fischer, MEd	Education
K Program Faculty Advisor:	Susan Greenspan, MD	Endocrinology
T Program Faculty Advisor:	Stephanie Studenski, MD	Geriatrics
CSTP Assoc. Director(Students)	Amber Barnato, MD, MPH	Preventive Medicine
CSTP Assoc Director (Resident):	Kathleen McTigue, MD, MPH	Internal Medicine

PhD Leadership Council	Mark Roberts, MD, MPP John Horn, PhD Greg Cooper, MD, PhD Judy Erlen, PhD Sandra Quinn, PhD Dan Siewiorek, PhD (CMU)	Internal Medicine Neurobiology Medical Informatics Nursing Public Health Computer Sciences	
Common Core Leadership Council	Sam Poloyak, PhD Mark Roberts, MD, MPP Sandra Quinn, PhD Lora Burke, PhD Mary Marazita, DMD Ellen Cohn, PhD	Pharmacy Internal Medicine Public Health Nursing Dental Medicine Rehab Sciences	
K30 CRTP Director: Co-Directors:  Associate Director:	Wishwa N. Kapoor, MD, MPH Robert Branch, MD Mark Roberts, MD, MPP Cindy Bruce, PhD	Internal Medicine Clinical Pharmacology Internal Medicine Health Services Research	
K12 CRSP Director Co-Directors:	Wishwa N. Kapoor, MD, MPH Joan Lakoski, PhD Doris Rubio, PhD	Internal Medicine Pharmacology Social Work	
T32 Director: Associate Director:	Wishwa N. Kapoor, MD, MPH Amber Barnato, MD, MPH	Internal Medicine Preventive Medicine	
Advisory Committees K12	Wishwa N. Kapoor, MD, MPH Silva A. Arslanian, MD Timothy R. Billiar, MD Robert A. Branch, MD Thomas W. Braun, DMD, PhD Gregory F. Cooper, MD, PhD Rory A. Cooper, PhD Jacqueline M. Dunbar-Jacob, PhD Michael J. Fine, MD, MSc Susan L. Greenspan, MD John P. Horn, PhD Joan M. Lakoski, PhD	Judith Lave, PhD Roberta J. Ness, MD, MPH Harold A. Pincus, MD Steven E. Reis, MD Charles F. Reynolds, III, MD James M. Roberts, MD Mark S. Roberts, MD, MPP Doris M. Rubio, PhD Stephanie A. Studenski, MD Ralph E. Tarter, PhD, MPA Stephen B. Thomas, PhD Michael J. Zigmond, PhD	Allied Health Bioinformatics Dental Medicine Economics/Pediatrics Endocrinology Epidemiology General Medicine Graduate Studies Health Policy Industrial Engineering Medicine Neurology Surgery
	K30 Timothy Billiar, MD Thomas W. Braun, DMD, PhD Jacqueline Dunbar-Jacob, PhD Mitchell Fink, MD Joan Harvey, MD Ronald Herberman, MD William Hogge, MD	Kristine Lain, MD, MS Judith Lave, PhD Alan Meisel, JD Charles F. Reynolds III, M Jeannette South-Paul, MD Stephen Thomas, PhD John Horn, PhD	Bioethics Cell Biology Critical Care Dental Medicine Family Medicine Health Policy Neurobiology
	T32	Representatives from SHS, PhD and Common Core Leadership Councils	All SHS
ICRE Board of Directors	Appointed by the Deans	All SHS	
ICRE Faculty Appointment	Application process	All SHS	

**D. 4. How these programs will enhance, shorten, and strengthen the training and career pathways for all clinical and translational research professionals.** Our extensive programs are specifically designed to accelerate and strengthen the pathway to independence as outlined below:

**Enhancing the interest and experiences of the investigators in the pipeline.** We have developed experiential and other programs for pre-college, undergraduate and pre-doctoral students. Our aim is to get students enthused about translational research by involving them early and providing early training so that they are ready to do research earlier than would be otherwise. This effort is likely to bring new investigators into CTS, strengthen their early training and shorten the time to begin their careers in research. Our proposal for a required common core in CTS for all pre-doctoral students will open doors to this discipline. Without this program, entry may never occur for some and may be delayed for others.

**Developing a Minority Career Development Program (MCDP).** We have designed a program for minority trainees interested in careers in CTS research while relatively early in training (e.g., residency and fellowship and post-doctoral). This program will provide these individuals with experiences in the conduct of clinical research and training and support in the development of research projects and corresponding proposals. The goal of the MCDP is to enable the trainees to jumpstart their careers by being able and ready to submit a successful K proposal to NIH immediately upon conclusion of their training.

**Predoctoral training in CTS.** Adding a certificate to any of the PhDs and more concentrated training (including PhD pathways) will strengthen the training in CTS for many predoctoral students who otherwise will not learn the methodology of the discipline and are at higher risk of failure. It will enhance the careers of predoctoral students interested in this field by providing strong training programs.

**Accelerating and shortening the pathway to independence of all CTS trainees.** Our entire effort in the K12 CRSP and CRTP has been focused on accelerating the pathway to independence. The effective elements of this effort will be migrated to all training programs including 1) student-centered didactic programs (individualized curricula) so that students avoid courses that do not advance their careers quickly, eliminating potential wasted time; 2) grant writing experience early in the students' careers to begin their



investigative careers earlier; 3) emphasis on working in multidisciplinary teams to allow them to effectively develop research which almost always requires working with individuals from multiple disciplines; 4) early emphasis on writing papers and presentations to help them learn to contribute to the literature and use that publication to begin new studies; 5) providing effective and closely monitored mentoring to help advance their careers and remove major blocks on their pathways; and 6) intervening on transitioning careers may actually eliminate the need for one or more postdoctoral years by helping them start planning investigative careers while in training (e.g., looking for funding, writing papers, writing grants, responding to RFAs).

**D. 5. How the institution will guarantee sufficient time for investigators to pursue clinical and translational research and mitigate the demands of providing patient care.** The Senior Vice Chancellor for the Health Sciences and the Deans of each of the SHS are committed to protecting the clinical investigators' time for research. At the University, which is a research-intensive school, a culture has firmly taken root that research time is sacred and protected. Each faculty and fellow's compensation is divided by percent effort into three areas: clinical, teaching and research. Clinical effort is supported by clinical income; teaching is supported by the hospital (for residency and fellowship) and by the Schools for student teaching; and research time is supported by grant funding or initial seed support by the departments. In the ICRE, we have established mechanisms which assure us that clinicians' time is protected for research. We will use similar methods in all of our training programs. The methods include: 1) a written commitment from the Department chair and Division chief about protected time for their trainees; 2) the program monitors the time protected for research closely, and 3) any issues or problems are discussed early with chairs or department chiefs and resolved. Using this method, we have been highly successful in assuring that protected time is provided for research. For medical students or predoctoral students in the SHS, protected time is guaranteed for those taking part in the short-term (2-3 months), one year program, and the PhD program. Similarly, for residents, our only limitations are regulatory RRC rules. Their time will be similarly protected as it is for other students. Fellows on T32s are entirely protected for their research time as support comes from the training grant.

**D. 6. Institutional incentives and rewards for new modes of team-based research that promote the academic mission.** The SHS have a culture of collaboration and team-based research is commonplace. The entire health care and research (all of the SHS and the Hospitals) enterprise is geographically in one location facilitating easy interactions among clinical and basic scientists as well as clinicians, patients, and investigators from multiple disciplines. Thus, even before the recognition of the importance of team-based research, this was a common practice at the SHS. There are several objective measures by which team-based research is incentivized and rewarded: 1) indirect costs on grants are returned to each investigator from different department or unit, thus, encouraging collaboration with others. The indirects can then be utilized for carrying out research by each member of the team; 2) promotion criteria recognize publications with others as first or senior author as important; generally a mix of first authored and team authored publications are viewed as ideal; 3) in the promotion process, not only grants as PI are viewed as important but working as a co-investigator on a team is also considered important; and 4) on major research days and at time of institutional recognition, the entire team is listed and recognized, and many members often participate in presentations.

**D. 7. Criteria for certification and degree programs.** These criteria are well defined by the University. Certificate requires 15 credits and evidence of research. An MSc degree requires a minimum of 30 academic credits and a thesis which in CRTP can be satisfied by one of three mechanisms as described under CRTP. A PhD degree requires 72 academic credits and an independent research dissertation (which accounts for 15 or more credits), preliminary and comprehensive exams. Requirements are very similar at CMU.

**D. 8. How mentors will be trained, evaluated, and replaced if necessary.** We view mentoring as essential to successful career development. Mentoring as well as the training, monitoring, and evaluation of mentoring have long been central to all of our training and faculty development programs.

**Mentoring Program Leadership.** While the SHS has an extensive tradition of mentoring, until a few years ago, much of it had been carried out informally with mentors serving as role models for future mentors. With the development of the CRTP and K12 CRISP, we developed formal programs for the selection and training of mentors and for monitoring the success of our multidisciplinary mentoring. Dr. Joan Lakoski, Assistant Vice Chancellor for Academic Career Development and Professor of Pharmacology, is the Director of the K12 CRSP Mentoring Program; this program will be expanded to become a major component of the CTSI. Dr. Lakoski founded the Office of Academic Career Development in 2002 and has led efforts among the SHS to support mentoring. Dr. Lakoski will lead efforts in mentor selection, training, evaluation, and intervention. She will be assisted by Dr. Megan Cunnane who will serve as Assistant Director of Mentoring. We have also developed a Mentoring Advisory Group (MAG) consisting of senior investigators, and we will expand this group to ensure sufficient representation of all the SHS. We have also established separate interest groups on mentoring women and minorities in academic medicine and these individuals serve as representatives on the MAG.

**The Mentoring Program.** All individuals involved in formal career development and training programs as part of the CTSI will require mentoring, and all mentors will be required to participate in the CTSI Mentoring Program. Mentoring will be provided for all trainees in all components of the T32 program. Mentoring is a central element of K12 Scholars (CRSP and BIRCWH) as well as to K30 trainees undertaking research projects and holders of T-type or K-type grants in the SHS. Trainees will be mentored by accomplished investigators who are actively involved in clinical or translational research, have active NIH funding, have established track records of mentoring, and are committed to the career development of the CTSI trainees.

The Director of the ICRE, working with Department Chairs and Division Chiefs, will help select mentors for CTSI trainees after meeting individually with the trainees and assessing their career goals and interests. Assistance of ACs and MAG will be sought. These individuals have very broad knowledge of the available mentors and have extensive experience in putting together multi-disciplinary teams. In collaboration with the trainee, we will select a primary mentor and co-mentors with complementary expertise. We will obtain a written commitment from the mentors to have continuous involvement with the trainees throughout the duration of the program and will provide them with clear expectations. Our expectation is that the entire mentoring team will meet with mentee on a regular basis to design and plan studies, discuss research progress, solve specific issues and problems arising during research, advise on project management, and help guide data collection, analysis, manuscript preparation, and other functions including the provision of career development advice.

**Mentor and mentee contracts.** The program will use learner-centered contracts with mentees. These contracts, which represent a well-recognized means of structuring the mentor-mentee relationship, allow the trainees to focus on the research areas of greatest interest to them and to create educational objectives consistent with these interests. The contracts also provide a formal mechanism for ensuring that progress is made in achieving the educational goals. The mentor-mentee contracts, currently used by the K12 CRSP and CRTTP, will be used to provide individual feedback to the mentors and mentee and serve as a tool for evaluation.

**Mentor and mentee training.** The goals of training are to provide a clear understanding of the purpose of mentoring, to delineate the expectations of the trainees, to develop consistent implementation of mentoring, to formalize the concept of team-mentoring, and to develop mentoring skills. The training is planned as an annual retreat designed to bring together trainees and mentors at the beginning of the program to get to know each other; to establish a sharing environment; to define roles and responsibilities; to develop agreements on the details of mentoring and the nonnegotiable aspects of the mentoring contract (e.g., the duration of the mentoring relationship, the frequency and location of mentor-mentee meetings, and the strategies used to value and reward time invested by the mentor); and to provide professional skills training (e.g., negotiation, active listening, questioning, goal setting, career planning, understanding communication styles, and feedback). We have developed three training modules: 1) Introduction to Mentoring for Mentees, 2) Introduction to Mentoring for Mentors, and 3) Team Mentoring. Due to the relatively large number of mentors and mentees involved with the CTSI, we expect to hold multiple training sessions at appropriate times throughout the academic year. All faculty who wish to serve as mentors for CTSI trainees will be required to participate in the training.

**Peer mentoring.** In addition to a senior mentor, some trainees will have a junior/peer mentor, drawn from K12 CRSP Scholars, K12 BIRCWH Scholars, K30 CRTTP trainees, and junior faculty. The peer mentor-mentee relationship has a number of attractive features. Foremost, it provides each trainee with a role model who is more proximate in age and training. There are many questions a predoctoral student or junior trainee might feel more comfortable asking a junior mentor, and indeed that a junior mentor might be in a better position to answer, such as how to choose a residency program. Additionally, it provides junior faculty, postdoctoral students, and fellows the opportunity to learn how to mentor formally, through structured mentor training, rather than simply by observing. We anticipate that by learning to mentor, junior mentors will be better equipped to maximize their own mentor-mentee relationships. Finally, this experience will allow us to accelerate the process by which mentees may become mentors which may be of particular importance for women and minorities.

**Short-term mentoring.** Students who elect the T32 short-term (2-3 month) practical research will have different mentor-mentee relationships than those electing the intensive training pathway. Importantly, the relationships may be of shorter duration. We will help students identify a mentor early, at least 6 months before starting their research rotation and have the relationship established no later than 4 months before the rotation. Early identification of mentors help with orientation to the mentors' research projects (by reading grants, protocols, and manuscripts and by attending research team meetings) and will maximize the students' chances of success with their own projects. It is expected that short-term experiences will be followed by several months (or years) of additional part-time work for manuscript submissions which we hope will promote informal ties with their research mentors throughout their career progression.

**Ongoing support of the mentoring relationship.** Through the Mentoring Program, we will monitor relationships and provide the support to accomplish the program's goals. Quarterly meetings of the mentoring team and the Mentoring Program leadership will allow for on-going oversight. Through an early evaluation and intervention process, we will determine if the relationship is not working. In such instances, the Program Director and Drs. Lakoski and Cunnane and the MAG will collaborate with the mentors and trainees to solve problems and develop alternative mentoring approaches. Should it be determined that a mentor-mentee relationship cannot be repaired, the Mentoring Program leadership will consult with all involved parties to determine the mentoring qualities and skills that are needed and identify an appropriate replacement. Our on-going monitoring will allow us to respond to issues and take required corrective actions in a timely fashion.

**E. Evaluation and Tracking.** Currently, we have a comprehensive evaluation in place for every existing component of our training programs including the K12 and K30 programs. We plan on extending this to the T32 and other new educational components (detailed in the CTSI *Tracking and Evaluation Plan*.) Our evaluation process includes a tracking system of all of the Scholars and Trainees. The application process that the Scholars and Trainees complete automatically registers them into the tracking system and is updated yearly. Tracking system captures extensive information (e.g., the program in which they are affiliated, the courses taken, and mentors' information). With tracking, we have data on enrollment and application (e.g., diversity of backgrounds, demographic data, disciplines, and specialties) and outcome measures (e.g., academic placement, type of research, publications, and others). The evaluation also includes surveys of the Scholars and Trainees about utilization and success, course evaluations, subjective and objective evaluation of mentors, the advisory boards, and the leadership of each program. Benchmarks for the effectiveness of the program will use the following short-term training outcomes (years 2-4 of the grant) and longer-term career outcomes. Short-term outcomes include the satisfaction with the program, the number of presentations, publications, and grants of Scholars and Trainees, and any changes in their academic rank. Long-term outcomes include percentage of effort in CTS research and grant funding on CTS projects as benchmarks, pursuing an academic career in CTS, and the extent to which they fulfill a leadership role in CTS.

We follow all of the trainees once they have completed the program. We regularly survey graduates to not only track their career success, but also to identify program features most useful in establishing their careers.

**F. Training in the Responsible Conduct of Research.** The University has made the responsible conduct of research a core fundamental clinical research training element required for submission of an NIH proposal, approval of an IRB protocol, or participation in a research project. Ethics and responsible conduct of research are integrated in many courses throughout the SHS and have become part of the fabric of clinical research. At the most basic level, the University requires that anyone involved in human subjects research (faculty, staff, and students) obtain certification from its online training program, "Research and Practice Fundamentals." The web-based, self-paced modules include Research Integrity, Human Subjects Research, Conflict of Interest, and HIPAA Privacy Requirements, and Responsible Literature Searching. Three of these modules, Research Integrity, Human Subjects Research, and HIPAA, are required prior to involvement in research.

Beyond this core training, other mechanisms are available for advanced training in the responsible conduct of research. CTSI researchers will be able to acquire advanced training through a number of programs. One of the premier training is a one credit course through the CRTP 2050: Ethics and Regulation of Clinical Research. This course presents an in-depth examination of the basic concepts, values, and policies related to the conduct of clinical research. Topics include the historical context for the scrutiny of clinical researchers and the formal mechanisms that are in place to guide researchers and protect the rights and well-being of research subjects, including issues related to privacy, confidentiality, protection of human and animal subjects, informed consent, and the IRB. Regulatory issues (from OMB, NIH, IRB, and others) pertaining to clinical trials and health services research are discussed as are topics such as subject selection; plagiarism and scientific misconduct; responsibilities of sponsors, monitors, and investigators; research with vulnerable populations, and ethical aspects of international research, as well as other conflicts of interest, authorship and presentation of data. The School of Nursing also provides training through existing courses (e.g., Ethics for Advanced Practice Nursing and Coordinating Clinical Trials). The School of Medicine provides ethics components in its existing courses, including: Ethics, Law, and Professionalism; Methods and Logic in Medicine; and Behavior, Illness, and Society. The School of Dental Medicine provides content related to research ethics in several courses including Professionalism in Dentistry and its series of three courses in Dental Research Design and Methodology.

Beyond the SHS, many trans-University programs provide instruction on research ethics and regulation. The CRHC offers at least two seminars yearly that focus on issues pertinent to research ethics. Some recent offerings have included: The Burden of Surrogate Decision Making Research and Scientific Integrity; The Implications of HIPAA on Human Subject Research; and The National Bioethics Advisory Commission's Report on Ethical and Policy Issues in Research Involving Human Participants; among others. The University's Survival Skills and Ethics Program provides graduate students, postdoctoral fellows, and faculty with formal

instruction in many of the professional skills necessary for success in one's career through a series of workshops. The Ask the IRB Seminar provides content related to human subject protections and new or imminent regulations and policies. All of these programs will be available to investigators and trainees in any of the SHS as part of the CTSI.

**G. Minority Recruitment and Retention Plan.** We have long recognized the importance of bringing minority researchers into the academic arena and have active programs within the ICRE to address this. We discuss here strategies we have taken and propose to continue under the auspices of the CTSI.

***Institutional strategies for meeting the challenge.*** The University has developed several initiatives for "pipeline" issues for minority candidates to help influence career choice and to increase a sense of self-confidence in young minority students. One such opportunity is the summer research electives for second year medical students and predoctoral trainees in the other SHS. In the medical school, the summer research elective has been institutionalized into a requirement for a scholarly project to earn an MD degree. This step is part of a larger institutional response at Pittsburgh to create longitudinal career development pathways for students who aspire to become physician-scientists, encompassing medical school, residency, fellowship, and junior faculty appointment. Through the CTSI T32 component proposed to provide short term research experiences for minority trainees and junior faculty, we will expand this program to all SHS.

***Faculty recruitment.*** To attract African American and Hispanic professional, we collaborate with the EXPORT Center at the GSPH (P60 award by the National Center for Minority Health and Health Disparities). We hosted, in 2005, the first Research Career Development Institute (RCDI) in Minority Health and Health Disparities. Attending were 28 minority post-doctoral trainees and junior faculty selected from an applicant pool of 38 from around the country. The RCDI was co-hosted by the developing EXPORT Center at the Jackson State University (JCU), a historically black university. The purpose of the RCDI was to help participants launch their research careers. The three-day workshop featured scientific autobiographies (case studies of building academic careers in minority health and health disparities research), a junior faculty panel of successful minority investigators discussing career launch, mentoring, academic career pathways in clinical research, key scientific issues in health disparities research, a case study of the successful Community Research Advisory Board at Pittsburgh (and its importance in promoting and sustaining community-based participatory research), key elements of a good research proposal, oral platform presentations, enactment of a mock study section focusing on three proposals by participants, negotiating for a faculty position, developing an effective CV, and strategies for writing and publication. The University subsequently successfully recruited two junior faculty in health services research who had attended this workshop. The second annual minority health disparities RCDI is planned for June, 2006, again jointly hosted by the University and JSU. ICRE is co-sponsoring the RCDI with Dr. Kapoor serving as an active partner in this Institute in recruiting minorities to CTS research careers.

To promote minority career development in clinical research, minority fellows, post doctorates, and junior faculty from all the SHS will be invited to attend RCDI. We believe that the RCDI will serve as a magnet to attract committed young minority researchers to Pittsburgh, to take advantage of the CTSI, the Center for Minority Health, and the extensive network of researchers and research training embedded in the University.

***Moving to the next level via the CTSI Minority Career Development Program.*** Through K12 CRSP we are developing a Minority Career Development Program (MCDP) to identify and work with potential minority scholars early in their predoctoral or fellowship years so that once they have completed their education, they are prepared to submit a competitive K or R grant proposal. We propose to expand this program to minority residents in the SOM and to minority pre-doctoral trainees in other SHS, resulting in the development the CTSI MCDP. We will identify minority trainees through the Graduate Medical Education Office and the Diversity Office in the SOM and through the Deans of the other SHS. All underrepresented minority trainees will be invited to participate in structured seminars and experiences in CTS to increase interest in CTS careers. CTSI will offer mentorship and guidance on the development of research proposals to trainees interested in careers in CTS. This will be accomplished through existing workshops and seminars on preparing for K awards offered through the OACD, the CRTP, the Survival Skills and Ethics Program and other units in the SHS. We also have a research development program through the CRHC, which we will offer to the minority trainees and faculty with the goal of developing high quality research proposals. We propose to expand and extend this program for minority residents, fellows, and post-doctoral trainees and pre-doctoral trainees with the intent that when these trainees are ready to accept a fellowship, post-doctoral, or faculty position, they will be ready to prepare, submit, and compete successfully for a K award at NIH.

**H. Research Education Component.** As noted above, we propose to extensively transform, expand and enhance the ICRE to become the premier site for CTS education in the nation. We have faculty committed to education as evidenced by the development of ICRE and its many programs. We have many senior mentors in the SHS who are committed to CTS Education as evidenced by our success in the K12 and K30

programs and in building the CSTP. The SHS are committed to the education component as noted by Dr. Levine who represents all of the SHS as the Senior Vice Chancellor for the Health Sciences.

**Pool of participants.** The growth of ICRE is testimony to the interest in clinical research. We are projecting 2-3 fold or greater increase in the participants in CTS education. The increased pool will occur as follows: a) all PhD students from all of the SHS will be required to take the common core curriculum; b) PhD programs in CTS will bring students from basic sciences, CMU, CRTP, Biomedical informatics to this field (approximately 16 doctoral students are estimated at steady state); c) enrolling at least 10 residents per year (from a pool of more than 1000 residents with 30 residents at steady state in the three year program; d) currently we have 25 medical students enrolled in a 5 year MD/CRTP program which will increase to 50 with students from other SHS; e) MSTP students will take CRTP curriculum (we estimate adding 5-10 students to the pool); f) Existing PhD programs will add certificate (estimate about 20 per year); g) program for coordinator and research staff involves the entire research enterprise and is potentially 1000s but training is limited; i) undergraduate and other programs are estimated in sections that describe them.

## **I. Predoctoral Research Training Component-T32**

**I.1. Program Overview.** We propose a Predoctoral T32 Program to provide core clinical and translational research training elements to all predoctoral trainees in the SHS, short term clinical and translational research experiences for pre-doctoral students, and a PhD in CTS for in-depth education in this area. We will also offer a Graduate Certificate for predoctoral students to acquire advanced training in CTS.

Developing a core curriculum and experiential requirements in translational and cross-disciplinary science arises from the belief that we can break down barriers through education about CTS and cross disciplinary communications. A proportion of predoctoral students may become interested in CTS if they are exposed to the field and learn about the opportunities in translational research. The development of the *core curriculum in CTS* is based on our commitment to transforming the education of *all* predoctoral clinical and science training programs at the SHS to include aspects of how the advancements in one discipline rely on foundations or advancements from another to maximize the integration of research discovery and clinical practice.

The common denominators for the clinical research training in the SHS are the skills that one must acquire to successfully establish a clinical or translational research focus. These skill sets include literature searching and evaluation, critical scientific thinking and creativity, study design proficiency, communication skills, technical proficiency, and research ethics and integrity. The goal of the CTSI Educational Core is to provide different levels of training in these skills via integration of the multidisciplinary course offerings in the SHS.

In order to accomplish this programmatic goal, we will develop a tiered approach to accommodate the needs of different types of trainees. The first level will be the development of a multidisciplinary core course that will be taken by *all* doctoral students during their predoctoral training. The second level will provide short-term practical experiences in the conduct of clinical and translational research. The third tier will consist of a graduate certificate in CTS for students in the SHS as well as interested faculty. Finally, the fourth level will include PhD Programs Described under D.1.1. This section of the proposal details the design of each of the other options.

**Tier 1: Clinical Research Training for all Doctoral Students in the Health Sciences.** This program, detailed in Section D.1.2. of this proposal will develop a two credit, team-taught, seminar-based core course that will be required of all professional doctoral students in the SHS titled *Introduction to Health Science Research: From Bench to Bedside to Community*. This will be one of the major components of the T32.

**Tier 2: Short-Term Practical Research Experience.** We will offer 2-3 months of full-time practical experiences in clinical research to selected predoctoral students from the SHS. The objectives of the short-term practical research experience are 1) to immerse students in an active CTS research laboratory or program so they can learn how clinical research is conceived, designed, implemented, conducted, managed, and analyzed; 2) to work closely with mentors and their research teams; 3) to carry out an independent multidisciplinary research project using the research infrastructure, program or data of the mentors and their research teams; and 4) to gain an introduction to clinical research and how it is conducted through introductory seminars and presentations. Details of the objectives and the curriculum for short-term experiences are presented below.

*Immersing students in a clinical research laboratory or program.* Each student will become an active member of a multidisciplinary research group in the CTSI and will participate in its daily or weekly meetings, seminars, and other activities. The student will work with the research staff to learn about how the study was designed, funded, and implemented. In general, we will promote multidisciplinary research through various centers and institutes affiliated with CTSI. Thus, the students will also have the opportunity to participate in the centers' conferences and seminars and interact with a larger group of investigators from multiple disciplines.

*Mentoring and becoming a team member.* Each student will have a primary mentor who is a senior faculty with independent research funding. The student will meet with his/her mentor weekly and all parties will sign mentor-mentee contracts concerning expectations and responsibilities. Since much of clinical research is

carried out in teams, students will interact with many of the team members, such as statisticians, data managers, data analysts, data entry personnel, laboratory technicians, and research nurses. Through these measures, we hope to enhance the research experience and make it productive and satisfying both for students and mentors.

**CTS research project.** Each student will carry out an independent research project during the short-term practical experience. The project will be based on existing data or ongoing research efforts. Working with their mentors, students will ask a specific question that can be addressed in a short period of time. We will strongly advise the students and mentors to pick questions from the mentors' projects that are feasible and can form the basis of an independent study by the students. The students will be required to write a short proposal that includes specific aims, a review of prior literature, significance and methods used to address the specific aims. They will develop analytic plans and address human subject issues as they work closely with the mentors and research staff. Since students will be selected for this program a relatively long time before they actually participate in the research practicum, we will encourage students to begin identifying and working with their mentors as early as possible so they can start their research as soon as their 2-3 month period begins. Students will be expected to be involved in the analysis and presentation of their research results. They will present their work locally on Health Sciences Research Day, will submit abstracts for regional or national presentations, and will be encouraged to write up their results for publication. They will participate in ongoing CTS seminars.

**Tier 3: Graduate Certificate in Clinical and Translational Research.** Students enrolled in any PhD program in the SHS can earn a Certificate in CTS, which will provide skills in CTS study design in a format that is adaptable to students enrolled in a PhD program. This format will allow for a greater impact in the training of students in the health sciences via its adaptability and focus on students' interests. A minimum of 15 credits are required for the certificate. Both didactic and experiential components will be required. Experiential components include co-mentorship and graduate committee representation from multiple disciplines.

**Experiential Training.** PhD students seeking the graduate certificate will be required to have an advisor and a co-advisor responsible for overall guidance of the student's graduate training. One of these individuals must be a member of the CTSI and the two advisors must be from different SHS. We will encourage selection of graduate committee member who is a CTSI faculty from a third SHS. This experiential component will promote novel multidisciplinary training within the various PhD programs of the health sciences.

**Table 4: Graduate Requirements in Clinical and Translational Science**

Didactic Requirements	Coursework	Credits
<b>Required common core</b>	Introduction to Health Science Research	2
	Clinical Research Methods	3
	Seminars in Clinical and Translational Research	1
	Ethics and Regulation in Clinical Research	1
	Introduction to Biostatistics	4
<b>Selected core</b> (select one)	Biostatistics: Statistical Approaches in Clinical Research	4
	Statistical Methods	4
	Genetics in Health Science Research (From GSPH)	4
<b>Elective Examples</b> (a minimum of 4 credits in the following types of areas)	Women's Health (GSPH)	
	Aging Research (GSPH, CRTP)	
	HIV/AIDS (GSPH)	
	Health Disparities (GSPH, CRTP)	
	Cardiovascular Disease/Diabetes (GSPH)	

**Didactic Training.** The didactic training (Table 4) is divided into certificate core courses, selective core courses, and elective courses totaling 15 didactic credit hours. The certificate core courses will be completed by all certificate students as a multidisciplinary group. These courses are required and are not multiple listing offerings. For the selected core courses, students will

select from several available options within the SHS. Finally, elective courses are designed to provide multidisciplinary course offerings that are specific to the student's research interests with the advice of the various representatives of the student's dissertation committee.

**Tier 4: CTSI PhD Program.** The CTSI PhD will be an integral part of the T32 program. Three PhD pathways are described in Section D.1 and include: 1) a basic science PhD augmented with a certificate in CTS, 2) a joint University of Pittsburgh-CMU PhD in Translating Research into Practice using training components of the Biomedical Informatics PhD program and CMU's Human Computer Interaction Institute, and 3) a new PhD program in Clinical Investigation based in the ICRE and developed through all of the SHS.

**I.2. Institutional Commitment.** The University is strongly committed to the development of highly trained clinical and translational researchers. This commitment is evident in the creation of the ICRE with the mission to ensure a continuous cadre of skilled clinical researchers by offering the highest-caliber training and education in clinical research to all level of trainees in the SHS, enhancing collaboration and cooperation among trainees and researchers from multiple disciplines, and expanding training opportunities in clinical research by further developing new programs and enhancing existing programs. As described previously, we currently have a number of very active clinical research training programs that meet the University's need to train clinicians and researchers at all levels (pre-doctoral students, residents, fellows, postdoctoral students, and faculty members). These programs are housed in the ICRE, thus fostering multidisciplinary interaction

and collaboration, promoting informal mentoring of trainees by trainees at different stages of their careers, and encouraging the use of multidisciplinary team approaches to examine research questions.

The University of Pittsburgh has institutional policies in place that promote clinical research careers. For example, very similar criteria for promotion and tenure are in place for clinical investigators and basic research scientists, with the result that a large portion of our tenured faculty are senior clinical investigators.

Additionally, the institution has developed mechanisms to use indirect cost recovery to provide faculty members with funding to support their research. This enables a faculty member to cross departmental boundaries without losing indirect funds to another department and brings needed recognition to co-investigators in departments other than that of the Principal Investigator. Recently the University has made major strides toward removing barriers to cross-disciplinary mentoring. In 2002, Dr. Levine established the Office of Academic Career Development (OACD), lead by Dr. Lakoski. In addition to many career development programs for predoctoral students, postdoctoral trainees, and junior and senior faculty, the OACD provides formal training in mentoring and is in the process of developing a proposal for the formal recognition and reward of mentoring.

**I.3. Faculty and Mentors.** The University has an extensive portfolio of research led by a highly accomplished and very large group of senior SHS faculty representing multitude of disciplines who will serve as excellent mentors. Currently approximately 40 faculty are active teachers in the K30 CRTP. To develop and implement the T32 and other educational components of CTSI (including PhD programs and elements for all pre-doctoral students) we expect to add another 50 faculty from all of the SHS. This eminent faculty will be supplemented by experienced investigators serving as mentors in all of the various components of the CTSI. Biosketches of 81 mentors currently approved by NIH as part of the K12 CRSP are included as part of this proposal as are biosketches of numerous other mentors who have agreed to serve in this capacity in this Institute.

**J. Mentored Career Development Component-K12.** The Multidisciplinary Clinical Research Scholars Program (K12 CRSP) is designed for individuals who have already received their doctoral degrees. We select applicants who are highly motivated, talented, and have received excellent training in their clinical content area. The Scholars are offered an outstanding, broad-based didactic curriculum using the CRTP program courses and seminars and other course offerings from the SHS. An experienced multidisciplinary mentoring team works with each Scholar on a research practicum to teach skills in research design, study management, grant writing, and other areas in the conduct of clinical research. Members of the Research Development Core (a shared facility, including an epidemiologist, statisticians, and data managers and analysts) works with Scholars in their research design and conduct, and the Multidisciplinary Advisory Committee (MAC) meets monthly to review and monitor the entire program and the Scholars' career progress. A comprehensive evaluation assesses the ongoing success of the program components and monitors the Scholars' success in research.

**J.1. The pool of potential K12 scholars and types of their prior research training.** We strive to select the best possible candidates from the local pool and nationally. One pool of applicants will be the trainees in the CRTP. The CRTP trainees have committed to careers in clinical research and many are planning multidisciplinary research, thus forming an ideal group upon which to draw. We have approximately 40 trainees entering the CRTP annually who may be eligible for the K12 CRSP. An additional pool for potential Scholars includes the hundreds of fellows and post-doctoral trainees in the six SHS, the majority of whom are not enrolled in the CRTP. We will have the opportunity to select from this very large pool the very best candidates who have elected to pursue a multidisciplinary clinical research career. Another pool of possible candidates is from T32 training grants. This pool is already accounted for among the CRTP trainees and they form a major portion of fellows in specialties and subspecialties. We will meet with program directors of T32s to describe the K12 CRSP and obtain assistance in identifying excellent candidates. The pool of candidates from outside Pittsburgh is also likely to be substantial since national searches for all fellow and faculty positions is the usual practice at the University. We anticipate no difficulty attracting applications from a large group of excellent candidates from outside. In each of the first two years of the K12 CRSP, we have recruited one scholar nationally.

**J.2. The criteria for scholar selection and evaluation.** The selected Scholars have a passion for multidisciplinary clinical or translational research and specific ideas about the areas they wish to study and what their future career paths will be. In a very competitive evaluation process, we select Scholars whose backgrounds show innovation and broad thinking. We believe that the selection of individuals who are open to and desirous of a multidisciplinary research career will pave the way toward a successful career development program. We select individuals at an early stage of their careers. Candidates are postdoctoral level trainees, fellows in their research years who are committed to careers in multidisciplinary clinical research, or junior faculty.

We select only those candidates who can commit at least 75% of their effort to research and training (with the exception of surgeons who must commit 50%) and we require written commitments from the department chair, the division chief, and the proposed Scholar for the protected time. In the first year of the program, we received more than forty applications from four of the five SHS for eight slots as well as applications from external candidates; four of our current scholars were fellows at the time of application and two are currently post-doctoral fellows; one scholar came to the University from Harvard to participate in this program.

CRSP candidates must prepare a brief proposal, describing their career development plans and their mentored and Scholar-initiated research plans. Applications are evaluated by the MAC and are rated on the following:

<b>Applicant:</b>	Is the applicant prepared, in terms of background and experiences, to undertake this program? Does the applicant demonstrate a plan to achieve short and long-term goals that would lead to a successful career in multidisciplinary clinical research? Does the applicant have a record of independent accomplishments that would lead to a successful research career?
<b>Career Development:</b>	Is the career development plan appropriate to the applicant's establishing a multidisciplinary CTS research career? Is the career development plan consistent with the applicant's previous training and career goals?
<b>Research Environment:</b>	Does the scientific environment in which the work will be done contribute to the probability of success? Is the applicant affiliated with a University Center, Institute or laboratory?
<b>Mentors:</b>	Do the mentors represent different disciplines, specialties or subspecialties? Do the mentors have sufficient experience in mentoring and conducting research? Have the mentors developed an adequate and appropriate team plan for mentoring the applicant?
<b>Institutional Commitment:</b>	Is the division chief or department chair enthusiastic about the applicant? Is the division chief or department chair committed to the applicant's long term career at the University? Is the chief or chair providing resources (e.g., seed, administrative support) to support the applicant's advancement? Do the other references show the applicant's ability to have a successful career in multidisciplinary clinical research?
<b>Research Plan:</b>	Does this study address an important problem?
<b>Significance:</b>	If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced?
<b>Approach:</b>	Are the conceptual or clinical framework, design, methods, and analyses adequate and feasible? Is the research plan appropriate to the applicant's stage of training and experience?
<b>Innovation:</b>	Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?
<b>Multidisciplinary:</b>	Does the research address issues using different perspectives of several disciplines, specialties, or subspecialties?

### **J.3. The career development plans for the prospective scholars and how the plan will be tailored to the needs of the prospective scholars.**

Our approach to developing a training program for each Scholar is that training must be customized to the individual Scholar. The CRSP Director, who is also the Directors of the ICRE, works with the MAC, the mentoring team, and Scholars to develop educational programs that are uniquely tailored to meet the needs and goals of each Scholar while ensuring that all Scholars have the mastery of a core didactic set of skills needed for multidisciplinary clinical research careers.

*Seminars in Multidisciplinary Research.* A year-long seminar series on multidisciplinary research has been created for Scholars. This seminar brings together Scholars and mentors from multiple disciplines together to discuss how research issues can be viewed from multiple perspectives of diverse disciplines. These seminars also explore issues related to investigators' responsibilities in clinical research, such as patient safety, protection of human subjects, compliance with regulatory requirements, and interactions with granting agencies and industry. This case-based seminar allows opportunities for collaboration, learning about institutional and NIH policies that affect investigators, and the development of publications and other products by the Scholars.

*Individualized Advanced Educational Program.* The Scholar, MAC members, mentors, and Program Director develop individualized advanced training experiences for each Scholar. Additional training often involves advanced clinical research methodology, learning about areas that are relevant to a Scholar's interest, basic science courses if the Scholar is interested in translational research, and courses in other disciplines that are critical to the Scholar's research endeavors and future concentration.

*Advanced Research Journal Club.* We are developing a special journal club for Scholars in their second and subsequent years of their training, which is directed toward the Scholars' presentations of their research (inception, progression, or completion), specific papers on research methods that cut across all of the disciplines, and the examination of issues surrounding mentoring and academic career development.

**Scholars' Research Program.** Each Scholar participates in two types of mentored research experiences, both of which are focused on a single disease or health problem, for up to 4 years (minimum of 1 year). In the first type of experience, the Scholars participate in an ongoing clinical research project and become an active team member, working alongside his/her mentors or team leader. In the second type of practicum, the Scholar designs and implements a new research project under the guidance of the mentoring team.

**Multidisciplinary Team Mentoring.** A mentoring team of at least two mentors from different disciplines supervises each Scholar, consisting of highly accomplished independent investigators who are actively involved in clinical research, an established track record of mentoring and providing research training, and are committed to the career development of the Scholar. Scholars generally have one to three other mentors, including research methodologists from multiple disciplines and content experts in the area of the Scholar's research. We provide training and on-going oversight to the mentoring process as described in Section D.8.



**J.4. The commitment of the applicant institution, the institution's research environment and the pool of mentors.** The leadership has indicated its commitment to research training in a number of ways:

**A Home for Clinical Research Education.** Recognizing the importance of interaction among trainees and mentors of different disciplines, the Senior Vice Chancellor for Health Sciences has created an **ICRE** and has provided a specific designated 12,000 square foot space for the Institute where investigators work together, hold seminars and meetings, and interact informally. This centralized space, which is separate from individual departments and divisions, has smart classrooms, cubicle space, conference rooms, faculty and staff offices and state-of-the-art computer facilities, facilitates the exchange of ideas, collaboration among trainees, networking, and provides experiences of working in a collaborative, multidisciplinary research environment.

**Career Advancement toward Independence in Multidisciplinary Research.** Because of the long period between grant application submission and funding, we begin addressing future research opportunities as early as is feasible. During the second year in training and beyond, the Program Director, MAC members, and the mentoring teams guide the trainees in formulating future research initiatives that will take them beyond the period they are involved with the training programs. We will promote multidisciplinary research grant development that will generally lead to RO1 applications but occasionally R21s and other types of grants.

**A Multidisciplinary Collaborative Research Environment.** The University has the clinical research infrastructure and capacity to address any and all clinical research questions using multidisciplinary and interdisciplinary approaches. Thus, scholars from multiple disciplines find a welcoming research environment in their schools and departments. Additionally, we have outstanding collaborative research through numerous institutes and centers, many of which are federally funded or have large number of federally funded multidisciplinary grants. The more than 90 research centers and institutes have training programs and methodological expertise in the entire spectrum of methodology needed for diverse areas of clinical research. The ICRE serves the function of linking the trainees to multidisciplinary groups and methodological expertise, thereby facilitating the development of a multidisciplinary and interdisciplinary workforce of the future, as envisioned in the Roadmap Initiative.

**A Pool of Mentors.** We have an extensive group of accomplished investigators for mentorship to Scholars and trainees in the CTSI. A sample of mentors is described and biosketches of prospective mentors are attached.

**J.5. K12 Mentors' Research.** To date, NIH has approved more than 80 mentors in the K12 CRSP representing many disciplines from all of the SHS. A brief description of mentors in the first group of Scholars:

Name and Titles	Topics of Research
Derek C. Angus, MD, MPH, Prof. Critical Care Medicine; Dir., Clinical Research, Investigation, and Systems Modeling of Acute Illness Lab.	Dr. Angus's research focuses on the epidemiologic, economic, and health services research aspects of critical illness and ICU organization and delivery. His studies examine: the incidence and outcome of the interrelated critical care syndromes of severe sepsis, acute respiratory distress syndrome (ARDS), and multi-organ failure; genetic risk factors and biomarker profiles for sepsis; traditional and novel ICU risk prediction tools; mechanical ventilation and end-of-life care; and large-scale translational research in acute illness.
Timothy R. Billiar, MD, Chair of Surgery and George Vance Foster Prof. of Surgery.	Dr. Billiar's research focused on inflammatory pathways following traumatic injury. His laboratory works with a broad array of models of injury and shock, ranging from liver cells in culture to large animal models. He first cloned human inducible nitric oxide synthetase, and is currently exploring the function of this gene in the liver working with models of hemorrhagic shock, ischemia and liver toxicity induced by tumor necrosis factor.
Gregory F. Cooper, MD, PhD, Assoc. Prof. Med and Intelligent Systems; Center for Biomedical Informatics.	Dr. Cooper's studies the application of decision theory, probability theory, machine learning, Bayesian statistics, and artificial intelligence to health problems. Projects include computer-based methods to assist in discovering biological pathways (e.g., gene-regulation) from high-throughput data (e.g., DNA microarray) and biosurveillance algorithms for early detection of disease outbreaks from commonly available electronic data.
Bernie J. Devlin, PhD, Assoc. Prof; Dir, Comput. Genetics	Dr. Devlin, a genetic epidemiologist focuses on the development of statistical methods for the analysis of complex psychiatric diseases and to discover the genetic basis of diseases and related phenotypes.
Douglas B. Fridsma, MD, PhD, Asst. Prof. of Medicine and Intelligent Systems in the Department of Medicine and CBMI	Dr. Fridsma is interested in developing computational tools based on formal organization theory and applying them to the study of technology introduction, clinical work processes, and collaboration between healthcare providers. He is currently involved in the clinical trials workspace for the Cancer Biomedical Informatics Grid project. The goal of this project is to develop open-source, standards-based interoperable software that will allow data collection and sharing among participating cancer centers funded by the National Cancer Institute.
Joseph T. Hanlon, PharmD, MS, Prof. of Geriatric Medicine.	Dr. Hanlon is involved in research concerning pharmacogeriatrics; pharmacoepidemiology; health services interventions aimed at improving drug therapy for older adults; the investigation of racial differences in drug use in older adults; and drug-related geriatric syndromes.
Lee Harrison, MD, Prof. of Med; Dir, Public Health Infectious Diseases Lab; Dir, Pitt Fogarty AIDS International Training & Research.	Dr. Harrison's research focuses on molecular epidemiology of HIV and bacterial agents. Projects include the transmission of vancomycin-resistant <i>Enterococcus</i> , <i>Pseudomonas aeruginosa</i> , and <i>C. difficile</i> within hospitals; molecular clones of <i>Neisseria meningitidis</i> causing invasive disease; community transmission of drug-resistant <i>Streptococcus pneumoniae</i> ; novel molecular subtyping methods for <i>Escherichia coli</i> O157:H7, <i>Salmonella</i> , and <i>C. difficile</i> ; and characterization of integrons in strains of multidrug-resistant <i>Salmonella enterica</i> .
John W. Mellors, MD, Prof. of Med; Chief, ID; Co-Director, Center for Viral Diseases.	Dr. Mellors' research on antiretroviral drugs has helped define the genetic and biochemical basis for HIV resistance to various nucleoside and nonnucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs) and foscarnet. His lab has developed new recombinant retroviral systems to detect and quantify drug-resistant HIV.
Mary L. Phillips, MD, Prof. and Dir. of the Functional Neuroimaging Program, Western Psych Inst and Clinic	Dr. Phillips studies the nature of symptom-specific abnormalities in the processing of socially salient information psychiatric illnesses. She uses functional magnetic resonance imaging to examine neural responses to emotions in normal and psychiatric populations. She is developing a comprehensive neurocognitive model of emotion processing and studying neural abnormalities predisposing to mood and anxiety disorders.
Steven Reis, MD, Assoc. Vice	Dr. Reis' research has focused on identifying pathophysiologic mechanisms of racial, gender, and

Chanc. for Clinical Research; Assoc. Prof. of Med; Dir. of Clinical Research for the Cardiovascular Institute.	socioeconomic disparities in cardiovascular disease (CVD). He was the first clinical investigator to report that estrogen acutely improves coronary artery endothelial function in postmenopausal women. Dr. Reis is currently studying racial differences in CVD risk factors, evaluating ways to improve CVD risk stratification in high-risk populations, and piloting a short-term intervention program to decrease CVD risk among African Americans.
Charles R. Rinaldo, PhD, Chair and Prof. of Infectious Diseases and Microbiology; Dir., Pittsburgh Multicenter AIDS Cohort Study (MACS) Testing Laboratory.	Dr. Rinaldo is involved in numerous areas of basic and clinical research. His studies of T cell immunity to HIV currently focus on the relationship of disease progression to dendritic cell function and to the reactivity of CD8+ killer T cells to HIV, human herpesvirus 8 (HHV-8), and hepatitis C virus. Notable findings from his research group include the following: human cytomegalovirus infects neutrophils in the blood and can suppress T cell immunity; CD4+ killer T cells are involved in immunity to herpesvirus, and they also help control HIV infection in persons with long-term nonprogressive infection; and others.
Thomas E. Rudy, PhD, Prof. of Anesthesiology; Research Dir., Pain Evaluation and Treatment Institute.	Dr. Rudy's major research interests include assessment and treatment of chronic pain, adherence to health care recommendations, the role of perceived control in adaptation to chronic physical disease and trauma, functional capacity testing of patients with pain and medical disabilities, and the use of modern psychometric theory to improve pain assessment and treatment outcome determination.
Titus Schleyer, DMD, PhD, MBA, Assoc. Prof. of Dental Medicine; Dir., Center for Dental Informatics.	Dr. Schleyer is a pioneering researcher in dental informatics and is involved in numerous projects concerning computer-based patient records, computer use in clinical dentistry, and educational software for dentists. He is now focusing on improving computer-based tools available to practicing clinicians and examining how clinicians interact with patient information before, during, and after patient visits.
Saul Shiffman, PhD, Professor of Psychology.	Dr. Shiffman's research focuses on cigarette smoking, nicotine dependence, smoking cessation treatment, smoking relapse, and situations that precipitate relapse episodes. He is currently examining the processes of smoking cessation maintenance and relapse in the context of treatment with a high-dose nicotine patch. They are also involved in a study whose goal is to develop and validate a laboratory model of smoking lapse episodes and in a study of less-than-daily smokers, who now constitute 25% of US smokers.
Asim Smailagic, PhD, Res Prof, Dir., Lab for Interactive Computer Systems and Wearable Computers, CMU	Dr. Smailagic has done pioneering work in the design and rapid prototyping of wearable computers and context-aware computing systems. His research focuses on computer architecture and coherent design of advanced computer systems. He developed methodologies for system-level synthesis and rapid prototyping; hardware-software co-designs; a speech recognizer and language translator smart module; and computer components that employ on-the-move collaboration, and real-time audio and video transmission over a wireless network.
Stephanie Studenski, MD, MPH, Prof. of Geriatrics, Allied Health, and Nursing.	Dr. Studenski's interests are in the evaluation and treatment of mobility disability in older adults. Her projects include a prospective cohort study of older adults and their primary providers to assess change in frailty over time; a clinical trial of exercise to prevent mobility disability in older adults with mild limitations; a prospective study of activity in older adults receiving treatment for cancer; a prospective study of balance, falls, and dopaminergic function in older veterans; and a clinical trial of erythropoietin in older adults with mild anemia.
Daniel E. Weeks, PhD, Prof. of Human Genetics and Biostatistics.	Dr. Weeks's research focuses on statistical human genetics and in developing new methods for mapping susceptibility genes involved in genetically complex diseases. This type of research involves developing algorithms and statistics, implementing them in computer programs, and testing them on real and simulated data.
Debra K. Weiner, MD, Assoc. Prof. Med.; Dir, Older Adult Pain Management Program.	Dr. Weiner is evaluating the functional impacts of chronic pain in the elderly, the effects of percutaneous electrical nerve stimulation (PENS) on chronic low back pain (CLBP) in older adults, and the effects of osteopuncture for osteoarthritis-associated knee pain and disability.
Huiying Yang, MD, PhD, Dir, Genetic Epidemiology Program; Assoc. Prof. of Pediatrics, UCLA.	Dr. Yang's research focuses on genetic susceptibility to common diseases. She has studied pharmacogenetic determinants of the response to angiotensin-converting enzyme (ACE) inhibitors for the treatment of hypertension, and she has explored methodological aspects of genetic epidemiology, including nonparametric and semiparametric approaches for fine mapping of genes with Hardy-Weinberg disequilibrium.

**J.6. Evaluation and Tracking.** We and the NIH have extensive plans for the evaluation of K12 CRSP. Evaluation plans are described in more detail elsewhere in this proposal.

**J.7. Role of the K12 CRSP Program in the CTSI.** The Roadmap K12 Multidisciplinary CRSP will serve an integral role in the CTSI. K12 will offer the best opportunity to develop the carriers of leaders in CTS as a discipline. This program is already a premier program at the SHS and is highly coveted. It will even become more critical to the success of CTS discipline at the University with awarding of the CTSA.

**J.8. Plans for support beyond 5 years:** We are fortunate to have strong Institutional support for clinical research training resulting in the provision of tuition reimbursement which, in conjunction with NIH training and career development grants, will allow us to move forward in our educational efforts.

**K. Timeline for Proposed CTSI Training, Education, and Career Development Programs** (grey areas show development phase; solid black areas show full implementation)

Programs	Year 1	Year 2	Year 3
Predoctoral Research Training Component-T32			
CTSI PhD Programs			
1 Translation: bench to clinical research Program			
2 Translation: Translating Research into Practice Program			
3. Doctoral Program in Clinical Investigation			
Clinical Research Training for all Doctoral Students in the SHS.			
Short-Term Practical Research Experience			
Graduate Certificate in Clinical and Translational Research			
Faculty Development Program			
Program for Coordinators, Research Nurses, Project Managers, and Investigators			
Program for research career (K) and research trainee (T) grantees			
CTSI Education for Residents			
CTSI Program for Undergraduates			
CTSI Education for Pre-College Students			
Mentored Career Development Component-K12			

***Transforming the Scientist:***  
**CTSI Design, Biostatistics, and Clinical Research Ethics Core**

To conduct effective clinical and translational research, investigators must have access to the expertise of methodologists, epidemiologists, biostatisticians, ethicists, and data managers who specialize in particular types and fields of medical research. For example, an investigator who wishes to conduct a randomized clinical trial of a new drug to treat an infectious disease needs to work with a team of methodologists, statisticians, and ethicists who are experienced in conducting clinical trials and have specific knowledge about the disease and its potential treatment outcomes. An investigator performing research in genomics requires a statistician who has worked in genomics. Well-established, well-funded researchers usually have an investigative team that includes experienced experts in methodology, data management, and biostatistics, but other researchers who are working with limited or no funding often face barriers to finding and receiving the appropriate expert help they need.

The University of Pittsburgh has numerous departments, centers, and institutes with members who have expertise and experience in design, biostatistics, and clinical research ethics concerning a wide variety of health related fields. Most established investigative teams are housed within a particular department, center, or institute and benefit from the expertise of other members of the same research entity. Although junior researchers could also benefit from this expertise, there is no formal mechanism for them to do so. Moreover, there is currently no central database of information concerning the research entities and the types of expertise that they could make available to researchers who are involved in designing clinical trials and translational research studies and in analyzing the results. No system is in place to prioritize the research being conducted, to ensure that the research designs are scientifically and ethically sound, and to ensure that the statistical analyses are appropriate. To address these issues requires a united effort of experienced collaborators from multiple disciplines with complementary expertise, as would be afforded by the Clinical and Translational Science Institute (CTSI) at the University of Pittsburgh.

As described in detail below, the Design, Biostatistics, and Clinical Research Ethics (DBE) Core of the proposed CTSI will undertake various activities to help junior and senior investigators overcome the barriers they face in finding and receiving appropriate data management, biostatistical, and epidemiological help and ethical guidance for their studies. These activities include the following.

1. The DBE Core will directly provide centralized services to trainees, fellows, and junior faculty who are conducting clinical and translational research studies and will educate them about these services.
2. The DBE will organize the University's many research entities into a network and will draw from this network to pair junior and senior investigators with appropriate specialized help in particular areas of study. Building a network that incorporates the diverse resources of the University will enable the DBE to achieve an economy of scale and effectively and efficiently offer services regarding data management, biostatistics, and epidemiology to a cadre of investigators with funded and unfunded research.
3. The DBE will organize a weekly seminar series that will bring together the members of the University network to share their experiences and develop ways to translate a wide variety of new tools and methodologies into current research. The DBE will also work with the CTSI Office of Clinical Research, Health Sciences and the CTSI Research Education, Training and Career Development Core to provide a seminar for trainees and CTSI Scholars on methodological techniques and issues with data analysis.
4. The DBE will conduct its own research on cutting-edge methodologies used in clinical and translational research. In addition to incorporating its results into the services it offers, it will present its work at national conferences and will publish its findings. We believe that the DBE activities will not only transform the way in which clinical and translational research studies are conducted at the University of Pittsburgh but will also lead to advances in the discipline of translational research at the national level.

**BACKGROUND**

The University of Pittsburgh has several data coordinating centers that investigators utilize to support their research. However, these services are not centralized. For example, the Roadmap K12 program has a part-time epidemiologist and a part-time biostatistician who support the Clinical Research (CR) Scholars. They also have programmers and data managers who help the CR Scholars with their data management needs and

someone to assist with their IRB protocol preparation and other issues. The GCRC has an Information Technology & Biostatistics Center (ITBC). The ITBC is an infrastructure support resource available to NIH sponsored investigators using all GCRC sites at the University. Another resource at the University is the Center for Research on Health Care Data Center. The Data Center provides data management and statistical support to a wide variety of clinical investigators across the University, providing state of the art technologies and methodologies for clinical and health services research. The Graduate School of Public Health has the nationally recognized Epidemiology Data Center (EDC); staff at the EDC support several multi-center clinical trials including the Bypass Angioplasty Revascularization Investigation and Type 2 Diabetes (BARI 2D) Study and the Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (VIRAHEP-C) Study. For examples of resources, see Table 1.

The University has a **Center for Bioethics and Health Law** (CBHL) to assist in the clinical research ethics component of the proposed DBE Core. Founded in 1987, CBHL brings together scholars and researchers from a variety of disciplines to cooperate in addressing issues in bioethics and law from both theoretical and clinical perspectives. The CBHL is founded on the premise that the questions posed by contemporary health care dilemmas are not the province of any single discipline but require the collaborative integration of insights garnered from history, law, medicine, philosophy, and the social sciences. The center is not a policymaking or advisory body. Rather, it is committed to in-depth analysis of the complex legal and ethical issues surrounding the health care process. One of the CBHL's functions is to foster collaboration between CBHL and non-CBHL faculty and clinical investigators in empirical research concerning bioethics and health law. Efforts are directed at identifying important legal and ethical issues arising from the provision of medical care and from the conduct of clinical research and at devising appropriate methods to study these issues. The extensive clinical facilities of the University of Pittsburgh Medical Center (UPMC) provide CBHL faculty with ample opportunities to analyze case records, conduct interviews of patients and health care professionals, and directly observe clinician-patient interactions. CBHL also participates in collaborative studies with other universities and institutions.

**Table 1. Selected Examples of Cross-Cutting Methodological Clinical Research Centers at the Schools of the Health Sciences**

<b>Center</b>	<b>Director</b>	<b>Number of Research Faculty</b>	<b>Disciplines/Specialties/Subspecialties</b>
Center for Bioethics and Health Law	Alan Meisel, JD, Dickie, McCamey, and Chilcote Professor of Bioethics; Professor of Law and Psychiatry	25	Anesthesiology, Communications, Critical Care Medicine, Elder Law, End-of-Life Care, Health Law, Health Services Administration, Human Genetics, Informed Consent, Internal Medicine, Neurosurgery, Pharmacy, Philosophy, Psychiatry, Public Health, Research Ethics, Sociology
University of Pittsburgh Cancer Institute	Ronald B. Herberman, MD, Professor, Director of University of Pittsburgh Cancer Institute and UPMC Cancer Centers	500	Internal Medicine, Hematology, Oncology, Immunology, Biostatistics, Informatics
Center for Research and Evaluation	Susan Sereika, PhD, Associate Professor of Health and Community Systems	2	Adolescent Health, Chronic Disorders, Critical Care, Genetics, Health Care Outcomes, Science, Statistics, Women's Health
Cardiovascular Institute and the Cardiovascular Research Center	Barry London, MD, Harry S. Tack Professor of Medicine	57	Cardiology, Critical Care, Electrophysiology, Internal Medicine, Nuclear Cardiology, Gender and Racial Disparities
Center for Research	Wishwa N. Kapoor,	58	Anesthesiology, Anthropology, Behavioral

<b>Center</b>	<b>Director</b>	<b>Number of Research Faculty</b>	<b>Disciplines/Specialties/Subspecialties</b>
on Health Care	MD, MPH, Falk Professor of Medicine; Professor of Health Policy and Management; Chief, Division of General Internal Medicine		and Community Health, Biostatistics, Business Administration, Children's Health Services, Critical Care, Data Management, Decision Sciences, Emergency Medicine, Epidemiology, Ethics, Gynecology, Health Economics, Health Policy, Humanities, Internal Medicine, Obstetrics and Reproductive Services, Occupational Health, Palliative Care, Pediatrics, Pharmacoeconomics, Pharmacy, Preventive Medicine, Psychiatry, Psychometrics, Pulmonary Medicine, Research Methodology, Rheumatology, Statistics
Center for Research on Health Care Data Center	Doris Rubio, PhD, Associate Professor of Medicine	10	Behavioral and Community Health, Biostatistics, Computer Sciences, Clinical Trials, Computer Services, Data Analysis, Economics, Education, Health Services Research, Information Science, Medicine, Psychometrics, Research Methodology, Social Work, Statistics
Epidemiology Data Center	Sheryl Kelsey, PhD, Professor, Department of Epidemiology	117	Biometry, Biostatistics, Computer Science, Data Management, Demography, Epidemiology, Health Services, Mathematics, Medicine, Nursing, Psychiatry, Psychology, Sociology
Magee-Womens Research Institute	James M. Roberts, MD, Professor and Vice Chair (Research), Obstetrics, Gynecology and Reproductive Sciences; Elsie Hilliard Hillman Chair of Women's and Infants' Health Research	88	Anatomy, Anesthesiology, Biochemistry, Biology, Biophysics, Cardiology, Cell and Molecular Biology, Cell Biology and Physiology, Clinical Epidemiology, Clinical Research, Dental and Oral Surgery, Developmental Genetics, Endocrinology, Family Medicine, Family Planning, Genetics, Gynecologic Oncology, Gynecology, Hematology, Human Genetics, Maternal-Fetal Medicine, Molecular Toxicology, Neonatology, Obstetrics, Oncology, Pathology, Pediatric Cardiology, Pediatric Pathology, Pediatrics, Pharmacology, Philosophy, Physiology, Psychopharmacology, Public Health, Pulmonary Medicine, Reproductive Biology, Reproductive Endocrinology, Reproductive Infectious Diseases and Immunology, Social Work, Sociology, Surgery, Toxicology, Urology, Vascular Physiology, Virology
Pittsburgh NMR Center for Biomedical Research	Chien Ho, PhD, Professor of Biological Sciences, Carnegie Mellon University	30	Biology, Cardiology, Computer Sciences, Engineering, Imaging, Immunology, Medicine, Neurobiology, Neuroscience, Pathology, Pediatric Critical Care, Pediatrics, Physical Chemistry, Physics, Surgery, Transplantation

**Table 2. VA-Funded Multidisciplinary Clinical Research Centers Affiliated with the Schools of the Health Sciences**

<b>Center</b>	<b>Director</b>	<b>Number of Research Faculty</b>	<b>Disciplines/Specialties/Subspecialties</b>
Mental Illness Research Education and Clinical Center (MIRECC)	Gretchen L. Haas, PhD, Associate Professor of Psychiatry; Director of the Family and Psychosocial Studies Program, University of Pittsburgh School of Medicine	60	Epidemiology, Genetics, Geriatric Psychiatry, Infectious Diseases, Internal Medicine, Neuropsychology, Nursing, Occupational Therapy, Pharmacology, Psychiatry, Public Health, Research Methodology, Statistics
The Pittsburgh Geriatric Research Education and Clinical Center (GRECC)	Steven Graham, MD, PhD, Professor of Neurology – Vice Chairman for Research; Director, Geriatric Research Educational and Clinical Center (GRECC) and Associate Chief of Staff for Research (ACOS R), VA Pittsburgh Healthcare System	8	Audiology, Biochemistry, Biostatistics, Geriatric Medicine, Medicine, Neurology, Psychiatry
VA Center of Excellence for Wheelchairs and Related Technology (WaRT)	Rory A. Cooper, PhD, Professor and Chair, Department of Rehabilitation and Technology	27	Bioengineering, Electrical Engineering, Epidemiology, Occupational Therapy, Orthopedic Surgery, Physical Medicine, Rehabilitation Medicine, Rehabilitation Science and Technology, Spinal Cord Medicine
VA Center for Health Equity Research and Promotion (CHERP)	Michael J. Fine, MD, MSc, Professor of Medicine; Associate Director, Center for Research on Health Care	34	Anthropology, Behavioral and Community Health, Biostatistics, Cardiology, Communication, Community Health, Epidemiology, Ethics, Geriatrics, Health Economics, Health Policy, Health Services Research, Infectious Diseases, Internal Medicine, Mental Health, Nephrology, Pharmacy, Psychiatry, Psychometrics, Pulmonary Medicine, Rheumatology, Sociology, Women's Health

In all the Schools of the Health Sciences, especially the School of Medicine and the Graduate School of Public Health, there exists strong departments in Biostatistics, Biomedical Informatics, Epidemiology, Statistics, and Psychiatry. These departments work with numerous clinical and translational investigators across the University. With their level of expertise, they are able to provide state-of-the-art collaborations with researchers and to engage in their own efforts to develop new methodologies.

The **Department of Biostatistics** in the Graduate School of Public Health is actively involved in designing new statistical methods and in collaborating on important research projects concerning cancer, cardiovascular disease, AIDS, childhood diseases, transplantation, evaluation of diagnostic imaging systems, and evaluation of treatment for medical and psychiatric disorders. The department is recognized for its contributions to the investigation of public health concerns associated with urban and industrial environments. These efforts are exemplified by the department's research into the evaluation of disease risk among workers exposed to

potentially toxic substances. To date, large-scale follow-up studies have evaluated the health risks of more than 250,000 workers in a wide variety of industries, including the steel, coal mining, automobile manufacturing, chemical, fiberglass, nickel, and pharmaceutical industries. The methodological approaches developed in these studies have served as models for national and international investigations involving large-scale occupational cohorts. Biostatistics faculty have also contributed to environmental quantitative risk assessment, emphasizing the use of statistical models to quantify cancer risks and the development of methodologies to facilitate the use of epidemiologic data for setting environmental standards.

The new **Department of Biomedical Informatics** in the School of Medicine will be led by Michael Becich, MD, PhD, and is supported by the Dean of the School of Medicine and the Chancellor of the University of Pittsburgh. This new Department will occur through the merger of the Center for Biomedical Informatics with the Centers for Pathology and Oncology Informatics and will be launched July 1, 2006. The strategic vision and mission statement for the new Department is to:

1. To provide national and regional leadership in innovation through research in Informatics
2. To provide the highest quality of support for the clinical practice of medicine through regional and nationally recognized Informatics support.
3. To provide the highest quality of instruction in Informatics. This is supported by leadership in national member organizations and national educational forums with deep commitments to training and education.

This program will serve as a resource for the DBE and has strong institutional support from the Medical School (\$1.9M) to support recruitment of new faculty. The new Department which will house the Center for Translational Informatics and has commitments for nearly 12,000 sq ft (available 4/1/06) and an additional 40,000 sq foot of new contiguous space that will be available in a two to four year horizon which will allow for consolidation of the three Centers.

Of note, the new Department of Biomedical Informatics is the home for The Biomedical Informatics Training Program which has 32 core faculty members who offer a wide variety of biomedical informatics courses for the 39 trainees in the Program. The trainees are diverse, comprising 13 physicians, 5 dentists, 3 librarians, 1 marine biologist, 1 medical informatician, 1 engineer, 4 computer scientists, 3 information scientists, 5 biologists/molecular biologists, 1 physical therapist, 1 with a background in public health and 2 nurses.

A major goal of the training and research program in the **Department of Epidemiology** of the Graduate School of Public Health is to develop techniques that will effectively reduce mortality and morbidity in specific communities. The major areas of concentration are chronic diseases, women's health, alcohol, aging, nutrition, telecommunications, and psychiatric, environmental, and molecular epidemiology. Research in the department involves many different populations. The studies concerning diabetes, for example, use data from the World Health Organization Center for Diabetes Registries and involve collaboration with investigators from 70 countries. The studies of the molecular epidemiology of insulin-dependent diabetes focus on susceptibility genes for diabetes in different populations. The nutrition and epidemiology program is a leader in clinical trials involving the prevention of kidney failure, colon polyps, hypertension, and coronary heart disease. The aging and chronic disease program is evaluating new methods of measuring cardiovascular disease, osteoporosis, stroke, depression, and dementia. The women's health program includes studies of menopause, obesity, exercise, diet, thrombosis, clotting factors, and behavioral attributes. The molecular epidemiology program focuses on chronic disorders and involves collaboration among the Departments of Epidemiology, Environmental and Occupational Health, and Human Genetics.

Founded in 1997, the **Statistics Department** is housed in the School of Arts and Sciences. Currently, its ten faculty are research leaders in statistical modeling and methodology in a variety of areas, including data mining, correction for measurement error, lifetime data analysis, meta-analysis, neurobiology, and time series. The department is now in the process of recruiting a new generation of faculty, expert in modern statistical computing techniques, who will continue its tradition of research leadership. The Statistics Department has developed very close ties with the Department of Psychiatry, with faculty being co-investigators on over a dozen grants from the NIMH. Two faculty hold joint appointments with Psychiatry; in addition, six graduate students and one postdoctoral fellow are supported for work on joint projects. In addition, The Center for Statistics provides statistical consulting services for researchers in all areas of the University of Pittsburgh community, and serves as an umbrella organization for all statisticians in the University by providing lectures, seminars, and professional short courses.

The **Department of Psychiatry** in the School of Medicine, with 185 faculty at Western Psychiatric Institute and Clinic (WPIC), is a national leader in clinical research, guided by multidisciplinary collaboration and

multiple responsibilities shared among treatment and research teams. A special emphasis is placed on ensuring that the research environment provides bridges to clinical treatment by focusing on the etiology of mental disorders, clinical treatment trials, methodological issues, and evaluation of outcomes. The Department of Psychiatry has 180 currently funded projects totaling more than \$77 million. The department houses five federally funded centers of excellence: the Mental Health Clinical Research Center for the Study of Affective Disorders; the Center for Functional Brain Imaging; the Obesity/Nutrition Research Center; the Center for Neuroscience of Mental Disorders; the Alzheimer Disease Research Center; and the Mental Health Clinical Research Center for the Study of Late-Life Mood Disorders. Several of these centers contain a fairly large data coordinating center within them. As such, these centers have experts in biostatistics, epidemiology, and data management.

Beyond the centers and departments within the University, several other resources exist that also provide services to investigators. The Office of Clinical Research provides support for unfunded research in the area of study design and statistical and epidemiological support. Additionally, other services exist for investigators that enable investigators to conduct secondary analysis. These are described below.

The **Office of Clinical Research (OCR), Health Sciences**, has created a prototype program, the Study Design and Statistical Consultation Service, to test the feasibility of providing services to junior investigators and other unfunded investigators such as medical students, residents, and fellows. The goal of this service is to support junior investigators in the acquisition of knowledge and skills necessary for their nascent research careers. This service has been staffed by two faculty with expertise in epidemiology, biostatistics, and education evaluation. The research projects in which the OCR is involved vary from evaluation of medical teaching methods to clinical trials, but they are predominantly translational studies. For investigators involved in clinical trials, the service provides advice on types of randomization schemes as well as preparing the randomization assignment for a study. Staff also review manuscripts, IRB protocols, and grant applications. Investigators requiring assistance outside the expertise of the staff are referred to other resources within the University or in the neighboring academic community.

The **Clinical Research Informatics Service (CRIS)**, was created by OCR in July of 2001 to provide consulting services to University of Pittsburgh faculty for clinical research data acquisition and analysis. CRIS is able to electronically extract and integrate data from a variety of UPMC data sources and provide this information to clinical researchers in a de-identified form. The large secondary sources of data can then be used for data mining. For example, investigators can use them to generate hypotheses, assess the feasibility of subject recruitment, and abstract patient data on research subjects. The **medical archival system (MARS)** is one example of such a data source.

MARS was developed at the University of Pittsburgh in 1986 to improve health care by integrating the computer systems that support medical care at the departmental level. The concept was to create a complete electronic medical record repository that would increase the efficiency of patient care, provide the basis for rational decisions about resource allocation, and support clinical research initiatives of the health sciences faculty. The initial focus of the program was on inpatient hospital care but is now extended to all patients seen at the UPMC's nineteen hospitals and 350 physician offices and outpatient clinics. In 1994, the MARS clinical database was integrated with the financial database from the UPMC billing system to include financial information. This financial database contains all inpatient and outpatient charges and payments at the UPMC. Longitudinal profiles of patient events can be created with direct links to all the elements of the clinical electronic record. A number of specific modules that have been developed for the MARS Financial System perform case mix studies, charge and cost profile studies, trend analyses, and profitability studies. Once a patient is identified as having an outcome of interest (e.g., an adverse reaction to a particular drug), the resources used during the patient's stay and their associated costs subsequent to the event can be retrieved. The current MARS repository houses 115 million clinical reports and 335 million financial transactions. Data are continuously fed into MARS over a network from sixty clinical and financial domains. An estimated 500,000 new clinical reports and 450,000 financial transactions are received each week. About 15,000–20,000 reports are retrieved daily for the support of clinical activity, and there are approximately 6000 logins each day.

Together with the Center for Biomedical Informatics, CRIS developed several tools that are useful to investigators. One important tool is **Data De-Identification (DE-ID™)** software, which is designed to locate identifiable information in records and to de-identify it before releasing the records to study investigators. The software is useful for de-identifying a narrative clinical report that is in electronic form, such as discharge summaries in the MARS repository (see above). Identifiable information, such as patient names, addresses,



physician names, and dates, are replaced with a tagged placeholder. De-ID is usually applied by an honest broke, who forwards the de-identified data to the research-project team. The De-ID software uses a set of heuristics to locate the presence of any of HIPAA's seventeen specific identifiers within electronically stored medical text. It locates the identifiers in the text by applying a set of rules at the sentence level. Identifiable information found multiple times in a report is consistently replaced with the same tag to improve readability of the report. For example, when a telephone number is removed, the tag "\*\*\*PHONE-NUMBER" is left in its place so the investigator can see that the type of information that was removed. Each tag begins with a double asterisk. The De-ID application has a configurable option for safe-harbor or limited data sets.

The Division of General Internal Medicine in the School of Medicine has an electronic clinical assessment tool that was created by the **Center for Research on Health Care Data Center**. All patients seen in the division's clinical practices complete the **Functional Assessment Screening Tablet (FAST)** as part of their routine clinical care. The FAST collects general screening information, such as data about tobacco use, quality of life, and additional data that can be used during the routine patient encounter. To date, nearly 10,000 patients have completed the FAST. At the end of the FAST, patients are offered the opportunity to participate in research studies. These include the division's Research Registry and Prospective Subject List, as well as other ongoing projects. The Research Registry permits information from the FAST to be combined with other medical record data for more comprehensive studies. The Prospective Subject List allows the Research Registry to be searched for inclusion criteria for other IRB-approved studies. About 2200 people have enrolled in the Research Registry and Prospective Subject List, and close to 100 have gone on to participate in other projects. Additionally, over 700 people have enrolled in other research studies directly from the FAST. This novel approach to data collection and management was one of the first research registries created at the University of Pittsburgh after the passage of the Health Insurance Portability and Accountability Act (HIPAA), which strengthened privacy requirements for both physicians and researchers. Researchers are able to utilize the Registry as well as the Prospective Subject List for recruitment.

The **RAND–University of Pittsburgh Health Institute (RUPHI)** is a collaboration between RAND Health and the University of Pittsburgh. RAND is a nonprofit institution that helps improve policy and decision making through research and analysis. RAND Health furthers this mission by working to improve health care systems and to advance people's understanding of how the organization and financing of care affect costs, quality, and access. Staff disciplines include economics, mathematics, statistics, medicine, law, business, physical sciences, engineering, computer sciences, and the full range of social sciences. RAND's newest office in Pittsburgh serves as a portal to RAND's work and to collaborators at RAND's other national and international offices. The RUPHI affords researchers the opportunity to combine regional talent with national expertise in helping to improve health services delivery and outcomes for a wide range of patient populations. The RUPHI seeks to empirically test and evaluate in the western Pennsylvania region the most promising interventions stemming from RUPHI's and RAND Health's research; identify potential clinical, organizational, and systemic barriers to the implementation of these interventions; devise and implement strategies to overcome such barriers; and demonstrate how to sustain the interventions in day-to-day community practice in the region and nationally. Responsive to both the national health care agenda and the needs of the local community, current RUPHI projects cross-cut several key areas: behavioral health; women's health; children's health; geriatrics and long-term care; and information technology and health.

### **Barriers to Accessing Services**

Although many departments, centers, and institutes at the University of Pittsburgh have expertise in ethics, methodology, epidemiology, and biostatistics, the University currently does not have a mechanism to coordinate these services and make them available in an organized manner to all of the researchers who need them. Most of the services described above lack the resources to help young investigators who are working under the auspices of career development awards or foundation grants and may be unfunded or underfunded. Typically, the methodologists, epidemiologists, and biostatisticians who work in the University services are required to have a certain percentage of their salary covered by research projects, and the remainder of their time is committed to teaching or administrative duties. Even investigators with RO1 grants frequently have difficulty finding a methodologist, epidemiologist, or biostatistician who has sufficient knowledge in the particular field they are investigating. For example, it can be difficult to find a clinical trialist to collaborate on an investigator's randomized clinical trial for 10% effort. A mechanism is needed to connect investigators with appropriate expertise.

## CORE DESIGN and METHODS

The University of Pittsburgh's experience with the Roadmap K12 Research Development Core (RDC) has demonstrated that providing an epidemiologist, a statistician, and data managers for the K12 Clinical Research Scholars dramatically enhances the quality of research that the Scholars are conducting. Since the Scholars have limited resources, the Roadmap K12 built an infrastructure to assist them with their research needs. This infrastructure not only provides data management and statistical support for their projects, but it also educates them about the best practices in clinical and translational research. The RDC trains Scholars in two ways. First, the RDC offers numerous seminars that enhance the quality of Scholars' research. Second, Scholars learn by working one on one with an RDC team member on their individual research projects. Through the RDC, Scholars learn about the importance of relational databases, data verification, and data dictionaries to issues with longitudinal data, missing data, and sample size.

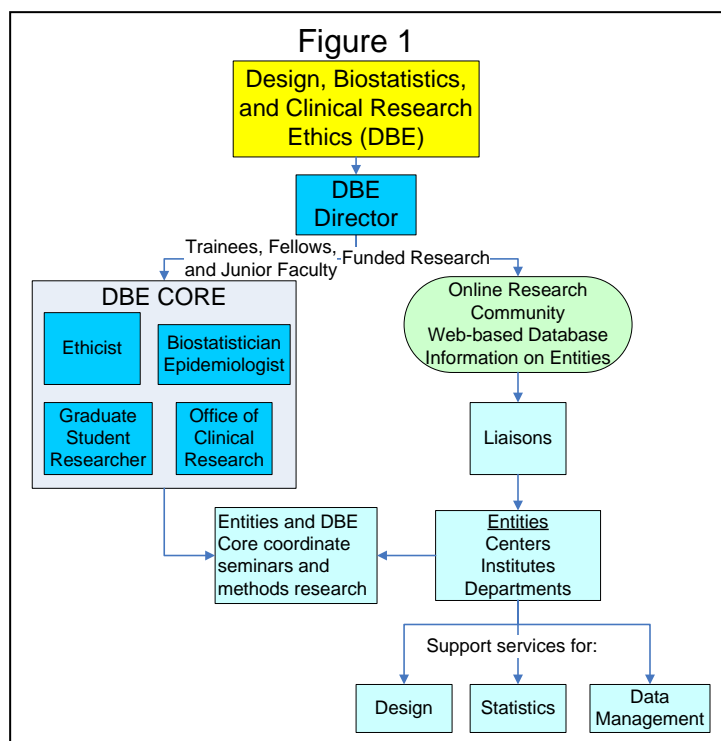
The CTSI proposes to build a large infrastructure similar to that in the RDC by creating a DBE Core that aims to 1) provide centralized services to a cadre of investigators conducting clinical and translational research; 2) develop innovative and creative research programs to develop tools and methods in design, biostatistics, and clinical research ethics; and 3) work with the CTSI Research Education, Training and Career Development Core to provide training and mentoring to trainees, fellows, and junior faculty, and to educate all investigators about the tools and methods developed.

### DBE Core Services and Organizational Structure

(Figure 1). The DBE Core will provide two types of services to investigators. First, its members will offer their own expertise in ethics, biostatistics, epidemiology, and data management to unfunded and underfunded investigators, such as trainees, fellows, and junior faculty. They will support clinical trial design and analysis and will ensure that all clinical and translational research designs are sound and that statistical analyses are rigorous and appropriate. Second, the DBE Core will extend its services to funded investigators by developing a mechanism to pair each investigator with appropriate services that are available from numerous "research entities," including the University and VA resources that are described above and listed in Tables 1 and 2. Many entities have already been identified and have agreed to participate in the DBE. As indicated in the numerous letters of support that are attached to this application, the entities are committed to and excited about partaking in this development of an integrated network of resources.

The DBE Core, along with the CTSI Center for Clinical and Translational Informatics, will create an extensive web-based system that contains information on the specializations and strengths of the various research entities. The DBE will have a Director, and each research entity will have a "liaison" who will work with the DBE Director and DBE Core. A liaison's role will be to identify the various strengths and areas of expertise of its research entity, to help the DBE Director connect investigators with the appropriate members in the entity, to collaborate on research with other liaisons, and to attend and present at the seminars that will be offered by the DBE Core. The Director, Core, and liaisons will form an advisory committee to address any issues that may arise.

As shown in Figure 1, the investigators will gain access to the services of an appropriate research entity through the DBE Director. It is anticipated that most investigators will be referred by CTSI Research Facilitators. After the investigator meets with the Director to determine the investigator's particular needs, the Director will search the web-based system for an appropriate research entity and will contact the liaison to coordinate services. The liaison will then facilitate the services that the investigator needs. Based on our



collective experience, we can categorize investigators into three groups, each requiring different types of services.

The first group consists of trainees, fellows, and junior faculty who generally do not have funding for their pilot research. Some of these investigators may have a K-award or are developing one. In this group, the investigators will generally not have funding for their research. Much of their research will be for their theses, pilot research, or career development award. As they embark on their research careers, the skills they develop now are critical to how they will conduct their research in the future. The DBE is committed to these investigators and propose that the members of the DBE Core work closely with them and train the investigators on the appropriate skills. In addition to offering the investigators data management and statistical services, DBE staff will counsel them about how to develop an operations manual, do reliability and validity checks on recruiters, and maintain the integrity of their research. The DBE will train them to conduct high-quality research and will work with them and their mentors to help bolster their career trajectories. DBE faculty will also work with the CTSI Research Education, Training and Career Development Core to provide seminars on the research topics they need.

The second group includes emerging investigators who are finishing their career development awards but are in need of data management and statistical support for a potential RO1 or a similar award. These investigators will require special services as they develop their proposal and conduct their research. The DBE will recommend a particular research entity for them to work with, based on the type and scope of the project, the specific needs of the investigator, and the specialization required to help the investigator form the best research team. In forming a team, it is critical to consider the strengths of the available experts and their knowledge and experience in the investigator's particular field.

The third group consists of senior investigators. These investigators usually have established resources to assist them with their data management and statistical needs. However, given the complexity of research in which they are engaged, they frequently encounter specialized issues requiring a high level of skill in a specific area. In these cases, the DBE will connect them with a research entity that has the necessary skills and expertise. In many situations, the investigative team will expand to incorporate another expert in the field. As the level of knowledge becomes more sophisticated in certain fields of clinical and translational research, this path will be increasingly utilized. This has the potential to tremendously enhance the caliber of research being conducted at the University, by sharing a high level of expertise among well-established researchers and expanding investigative teams. Collaboration across the University will greatly expand.

### **DBE Core Staff**

**Director**, Doris Rubio, PhD will serve as the Leader of the DBE providing oversight to this core of the CTSI. She will be responsible for the supervision and coordination of data and statistical services offered by the DBE. She will work in close communication with the Core Leaders, Drs Bost and Barnard as well as the liaisons for the entities. Dr. Rubio is currently the Director of the Data Center for the Center for Research on Health Care, Co-Director of the Roadmap K12 Program and an Associate Professor of Medicine at the University of Pittsburgh. She received her Ph.D. from Washington University in St. Louis. She was on faculty at Saint Louis University and tenured in the Department of Research Methodology for six years prior to being recruited to the University of Pittsburgh. As Director of the Data Center, Dr. Rubio has consulted on numerous clinical and translational research studies. In this role, Dr. Rubio serves as a liaison between the data management team, statistician, and the principal investigators. She part of the core faculty of the K30 program and teaches Biostatistics, Regression and ANOVA, and Nonparametric Statistics. She serves as a statistician for the Research Design and Development Seminar, working with trainees to help develop their research proposals. She has developed a grant for fellows in General Internal Medicine so that they can use the Data Center to help them with their research projects. Dr. Rubio works closely with these fellows in order to ensure the quality of their research and to train them on the best practices in clinical research.

**Statistician**, James E. Bost, PhD will serve as the Senior Statistician in the DBE and will provide consultation support to pre-award activities and conduct data analyses of unfunded studies. He will participate in development activities focusing of research design and methodology including data analysis. He will also collaborate on methodological initiatives initiated by this core. Dr Bost received his PhD in Research Methodology from the University of Pittsburgh in 1992 and his MS in Statistics from The Ohio State University in 1988. Prior to joining UPMC, Dr. Bost was an Associate Professor of Biostatistics at the University of Arkansas for Medical Sciences (UAMS) and the Associate Director of Health Data and Statistics at the Arkansas Center for Health Improvement. While at UAMS he established the Arkansas Health Data Initiative which

continues to bring together health care data from private and public sources to monitor and improve health care for Arkansas residents. Dr. Bost also served for five years as the Assistant Vice President of Research and Analysis for the National Committee for Quality Assurance (NCQA), a managed care watchdog organization. At NCQA he and his staff measured health plan performance using clinical and survey data and reported results used by both consumers and employers when making health care decisions.

**Ethicist**, David Barnard, PhD will serve as the clinical research ethicist for the DBE. He will provide consultations services to unfunded and funded investigators. As a faculty member in the K30 program, Dr Barnard will also instruct trainees on ethics and regulations in clinical research. Dr Barnard received his Ph.D. in Religion and Society from Harvard University in 1980. For twenty-five years he has taught bioethics and humanities at academic medical centers, having served as President of the Society for Health and Human Values in 1991-1992, the oldest and largest national organization for bioethics and medical humanities. He was chair of the Department of Humanities at Penn State University College of Medicine from 1988 to 1999. Since moving to the University of Pittsburgh in 1999 he has been a core faculty member of the Center for Bioethics and Health Law. He is course director of the required course Ethics and Regulation of Clinical Research for the Clinical Research Training Program.

### Support for Clinical Trial Design and Analysis

A resource pool of systems analysts, database managers, data analysts, statisticians, ethicists, and programmers with bioinformatics training will be assembled to work with all of the CTSI investigators in the conduct and management of their research programs. Along with the Education Core, these experts will work to ensure that investigators receive appropriate help and training in conducting clinical research. Table 3 below illustrates essential components of the management of one type of clinical research study and shows how DBE faculty and staff will serve as team members. It also shows how they will be involved in all phases of the study but to a varying degree.

**Table 3. Clinical and Translational Study Management Personnel Utilization**

Study Time Sequence	Investigator	Epidemiologist	Statistician	Study Coordinator	Systems Analyst	Database Manager	Ethicist
Protocol design	XXX	XXX	XXX	XXX	XXX		XX
Hypothesis testing	XXX	XXX	XXX				
IRB protocol and consent forms	XXX			XXX			XXX
Database design	XX		X		XXX	XXX	
Subject identification/ Recruitment	XXX	X	X	XXX	X		XX
Questionnaire	XXX	X	XXX	XXX	X		X
Tracking of subjects	XX			XXX	XXX	XXX	X
Database management	X				XXX	XXX	

\*The anticipated level of activity of each team member is: X = limited; XX = moderate; and XXX = high.

Before an investigator initiates a study, the DBE epidemiologist, statistician, and staff will meet with the investigator to review the project and to clearly outline the study goals, research design, and analytic methods for the proposed study. This will enable the DBE team and investigator to determine the data services needed to support the various processes involved in data management and processing (e.g., the development of paper-based and paperless data collection forms, the creation of data dictionaries and codebooks, the verification and entry of data, the use of data validation checks and methods for error checking, and the implementation of safety reports).

Early involvement of a bioethicist will help the investigator anticipate and prevent potential ethical problems or human subject protection concerns at the level of protocol design and development, rather than waiting until problems arise with actual subjects. This early involvement will also increase the efficiency of protocol development by streamlining the process of IRB review and building in safeguards on the basis of the anticipated problems or concerns.

DBE faculty and staff will provide assistance in IRB protocol preparation, development of consent forms, and subject recruitment. They will also train study teams in data collection, data screening, data coding, data entry

and verification, the manipulation and archiving of data, and the monitoring of study progress. By working closely with investigators on their research projects, DBE faculty and staff will become integral members of the research teams. The statisticians and epidemiologists will continue to work closely with the investigator on manuscripts and presentations as well as in the next phase of preparing grant proposals.

For investigators working with clinical trials, several tools are available. First, the CTSI Center for Clinical and Translational Informatics (CCTI) has a Clinical Trials Management Application (as discussed in the CCTI section) that can help investigators manage their clinical studies. Second, the Center for Research on Health Care Data Center has created an electronic data management system for clinical trials. This system (the FAST system, described above) enables researchers to collect data directly onto a tablet PC while recruiting participants in the field. The software seamlessly randomizes participants so that even the interviewer can be blinded to study assignment. Also built into the software is a tracking system with call logs, email reminders, and programmed calendars that enable the investigator to follow up with participants at different time points, depending on the design of the study. The software is customized for each study so that extensive protocols with branch logic can be implemented. A real-time reporting component provides investigators with up-to-the-minute information on recruitment, follow-up rates, and data safety monitoring issues. Third, the staff of the Epidemiology Data Center (EDC) have extensive experience in creating software systems when commercial software cannot address a specific need. Since its establishment in 1980, the EDC has focused on building software systems in-house to provide data management infrastructure for research (e.g., MATRIX, PoP, and Project Web portal systems).

Statistical Assistance for the Pediatric Clinical and Translational Research Centers (CTRC). This CTRC will transform the traditional inpatient GCRC to a pediatrics research network by incorporating the present GCRC in and outpatient resources with outpatient networks of the Children's Hospital of Pittsburgh. Any investigator interested in doing research involving children will be able to work with the pediatric CTRC for statistical help. Given the recent history of use of the Office of Clinical Research for statistical support by pediatric researchers and the requirement that every pediatric resident perform a scholarly project, a statistician that supports this effort can assist a wide group of users.

### **Educational Tools to Instruct Trainees.**

The University of Pittsburgh's experience in working with trainees, fellows, and junior faculty in the existing K12 and K30 programs, suggests that young investigators are better served if they are actively involved in data management and statistical approaches to clinical and translational research. If services are merely provided for them, they will be less likely to understand the rationale behind the best practices of data management and statistical analyses (e.g., the need for double data entry and verification, the need to reinterview a portion of the sample for validity checks, and the need for methodological rigor in conducting analyses), and they will be less likely to be able to incorporate these practices into their future research. The DBE approach will therefore be to have experienced statisticians, epidemiologists, and ethicists work directly with trainees, fellows, and junior faculty in order to guide them in developing and conducting their research and to train them about best practices. In addition, the trainees will participate in formal educational seminars.

Currently, the Office of Clinical Research (OCR), Health Sciences has monthly seminars designed to help junior investigators improve their research. The DBE will collaborate with the OCR and the CTSI Research Education, Training and Career Development Core by contributing to the seminar series, introducing investigators to advances in methodological techniques, and discussing common topics such as issues with analyzing correlated data, finding solutions for missing data, and exploring different methods for randomization. In addition, the DBE will develop a new weekly seminar series to bring together investigators from the various research entities to share their findings, to advance the use of new methodologies, and to translate research into practice. Given the amount of methodological research that currently takes place across the schools of the health sciences, a forum is needed to bring members of the various research entities together on a regular basis to discuss projects and develop new collaborative efforts. Such topics as alternative designs to randomized controlled trials, mixed modeling, and multivariate joint modeling will be discussed. Both the monthly seminar and the weekly seminar will utilize the learning components of the Online Research Community as proposed by the Biomedical Informatics Core, such as live webcasting and archiving of presentations.

Another mechanism that the DBE Core will use to educate trainees relates to two T32 programs in the Department of Biostatistics. The first program, entitled Predoctoral Research Training Grant in Biostatistics, is funded by NIGMS and is directed by Dr. Howard Rockette, Chair of the Department of Biostatistics. In this

program, a biostatistics trainee participates in approximately five rotations, each representing a different discipline. At each rotation, the trainee has a clinical mentor. The DBE Core serve as one such rotation. In this way, the DBE can mentor trainees who are working on their PhD in biostatistics. It is anticipated that the DBE Core will be exposed to a variety of research projects that involve both clinical and translational research. With strong mentoring that we can provide, this would make for an exceptional trainee experience. The second T32 program, entitled Training Biostatisticians in Psychiatric Research, is funded by the NIMH and is co-directed by Dr. Sati Mazumdar of the Department of Biostatistics and Dr. Charles F. Reynolds of the Department of Psychiatry. The DBE will work with Drs. Mazumdar and Reynolds so to provide additional training experiences for these T32 trainees.

### **Approach to Prioritizing Research Projects.**

As investigators formulate their research agenda, the DBE will encourage them work with the DBE Core. This will enable us to transform ideas into feasible studies. No study will be supported by the DBE Core unless it meets the following DBE prioritization criteria:

- Scientifically, ethically, and clinically relevant (e.g., has health importance, financial importance, and evidence-based support);
- Feasible (e.g., the required sample size is attainable given the subject population and financial constraints);
- Scientifically and ethically sound (e.g., conforms to ethical principles articulated in the Belmont Report and incorporated in federal regulations, is HIPAA compliant, and is based on appropriate animal studies or pilot study results).

In order to implement the prioritization of research, the DBE will develop a specific process that investigators must follow. First, investigators will submit their ideas to the DBE Core in the form of project aims and hypotheses, subject or data availability, and a description of how the project relates to the mission of the CTSI and their own research agenda. If investigators are trainees, fellows, or junior faculty members, they will need to provide evidence that their mentor believes the study is clinically relevant and scientifically and ethically sound and that their mentor is prepared to meet and work together with the DBE Core. Second, the DBE Core will work with investigators to determine the feasibility of the project and determine whether the needed study team can be assembled and would be available at the level of effort needed for the duration of the study. The DBE Core will also review the proposed study for potential ethics and HIPAA concerns and propose ways to address these. The DBE Core will then review the study with the investigator in order to assist in the development of a proposal that will include the aims and hypotheses, a brief description of the methods, and an outline of the particular data management and statistical needs. This description can then be circulated to other entities when appropriate.

The DBE Core will create standardized reports on subject recruitment, database development, data collection, and interim monitoring of stopping rules and loss to follow-up. It will also implement a “red phone” response system in the event of critical problems associated with the study that could signal potential ethics violations, immediate need to stop the study, critical flaws in the database design, or flags that critical deadlines will not be made.

### **Clinical Research Ethics.**

Clinical research ethics will be integrated into the research enterprise both proactively and on a consultative basis. Proactively, the ethicist will maintain regular contact with research mentors and directors of research teams in order to keep track of emerging research studies and protocols that are likely to present ethical concerns, either because of the risk-benefit ratio, the vulnerability of the potential study population, or the complexity of the consent process. The ethicist will then be available to participate in regular meetings of the research groups during the period of study design, to anticipate ethical issues, and address them preventatively. At this level the ethicist's involvement will include assessment of alternative experimental designs, eligibility requirements, and development of consent forms.

Consultative services will also be available to investigators who request help analyzing ethical aspects of study design or with the informed consent process. These services will be complementary to, rather than a substitute for, the current pre-review outreach activities of the Institutional Review Board. It is envisioned that some investigators will have concerns about how to integrate feedback or requests for protocol revision from the IRB in ways that respect the integrity of their research objectives. The DBE envision the ethicist as an additional

resource to the investigator at this point, thereby minimizing conflicts with the IRB or accelerating their resolution.

In addition to helping individual investigators with their research, the DBE Core will have the capacity to undertake its own original studies on ethical aspects of clinical research. Two examples are discussed here.

The first example concerns a persistent problem with the informed consent process in clinical trials. This problem is the “therapeutic misconception,” in which subjects believe (erroneously) that the treatment they will receive in the trial will be selected on the basis of the investigator’s belief that this is the best treatment for them individually, whereas in fact the treatment is selected randomly. Studies show that the misconception persists despite nearly universal agreement by investigators that subjects’ consent should be “fully informed” and despite the fact that information about random selection of treatment is routinely included in written consent documents. The DBE Core proposes to address the problem in collaboration with other ethicists, communications researchers, and health services researchers, by comparing different communications styles and strategies of investigators to answer three questions: 1) Does the investigator’s communication style affect the likelihood that the therapeutic misconception can be reduced? 2) Can optimal communications styles be taught to investigators? 3) Will investigators incorporate optimal communications styles into their routine interactions with subjects once they have learned them?

The second example concerns the concept of minimal risk. Despite considerable effort to clarify it in the research ethics literature, this concept continues to frustrate investigators and IRB members who try to apply the concept to research on children. There are at least two aspects to the difficulty. The first is the inherent ambiguity in the frame of reference for the “minimal risk” standard—that is, should the risks be those of a child’s everyday life, should the everyday life refer to that of a healthy child or a child with a particular condition, and so on. The second aspect is, for any given frame of reference, how to apply it to any particular intervention or study design. As a result of these difficulties, IRBs continue to pass inconsistent judgments on pediatric research protocols, with the consequence that some worthy protocols are probably rejected when, by an equally reasonable interpretation or application of the standard, they could have been approved, and vice versa. We propose a collaborative study of the interpretation and application of the concept of “minimal risk” and of the related concept of “minor increase in minimal risk” by pediatric researchers and IRBs, intended to address the following questions: 1) What frames of reference do IRB members and investigators use to interpret and apply the standards? 2) Can investigators and IRB members achieve agreement on the application of the standards to a variety of proposed research interventions? 3) What steps can IRBs and bioethicists take to improve the level of agreement and consistency of application of these standards?

### **Resources to Develop Tools and Methods in Clinical and Translational Research.**

Novel clinical and translational research requires the development of new approaches to data collection, analysis, and reporting. The DBE Core, along with the research entities, will be able to assemble a team of experts in a needed area of study and submit methodological development proposals to support the current and future needs of investigators.

The DBE Core has several topics in mind for investigation. First, a study could be conducted to investigate the applications of multivariate longitudinal models in clinical investigation. In many clinical and health service investigations, participants are followed over time with responses measured longitudinally, and sometimes with a survival end point. An important research objective in such studies is to find predictors of a final outcome, such as recurrence of an illness. In some situations, the predictors can be a trajectory of recovery during a specified period of time. Established statistical methods such as cluster analysis fail to capture the unique profile of responses on individual levels, and models utilizing the whole trajectory as predictors for final outcomes are needed. Second, research could be conducted to improve statistical models used in clinical research in which longitudinal and survival outcomes are measured concurrently. For instance, in HIV clinical trials, CD4 count curves and survival outcomes are both measured. In such cases, a two-step statistical model is not appropriate due to bias caused by early events. Third, research could explore causal inference with mediation and moderation analysis of longitudinal data. This type of analysis is very useful in clinical research, but most approaches can only handle cross-sectional data. New techniques need to be developed to handle longitudinal data, such as a nonlinear mixed-effects model to improve the statistical inference in causal modeling through mediation and moderation analysis.

To help initiate the development of the DBE research program that focuses on tools and methods in design, biostatistics, and clinical research, the DBE Core proposes to conduct a pilot study in the first year of the CTSI. Coordinating with the research entities, the DBE will develop a prioritization scheme to assist with selecting

the most appropriate topic. The DBE will then solicit proposals from the investigative teams to conduct the research. As part of the funding requirements, the investigative team will be asked to present its findings at the seminar we are proposing with the research entities. After the first year, we will help facilitate submissions of these proposals to the Pilot Studies Core.

### **Evaluation/Outcome**

To provide the most effective and efficient services, we must constantly monitor our efforts. Since services will be provided by the DBE Core and other entities, we will develop a consistent manner of evaluating and reporting the progress of each investigator's study. Many of the entities already have monitoring systems in place, and we will begin by identifying the strengths and similarities of these systems. We will develop and incorporate methods to ensure that the data management, statistical support, and other research support are acceptable. For example, we will develop mechanisms for the investigators to 1) directly inform the DBE of staff issues, 2) ask for an additional team member with a skill set not previously identified as needed for the study, and 3) request a consultation with DBE team on problems or issues not foreseen and how these can be solved. Any issues that arise from the evaluation will be presented to the advisory committee that is comprised of the director, core and liaisons. They will regularly review the evaluation efforts and implement any changes that are needed. For additional details, see the *Evaluation and Tracking Plan Section*.

### **Transforming Elements**

The activities of the Design, Biostatistics, and Clinical Research Ethics (DBE) Core are designed to help trainees, fellows, junior faculty, and senior investigators overcome the barriers they face in finding and receiving appropriate data management, biostatistical, and epidemiological help and ethical guidance for their studies. First, the DBE Core will directly provide centralized services to young investigators who are conducting clinical and translational research and will educate them about these services. Second, the DBE will help organize the University's many research entities into a network and will draw from this network to pair investigators with appropriate specialized help in particular areas of study. Building a network that incorporates the diverse resources of the University will enable the DBE to achieve an economy of scale and to effectively and efficiently offer services regarding data management, biostatistics, and epidemiology to a cadre of investigators with funded and unfunded research. Third, the DBE will organize a weekly seminar series that will bring together the members of the University network to share their experiences and develop ways to translate a wide variety of new tools and methodologies into current research. Fourth, the DBE will conduct its own research on cutting-edge methodologies used in clinical and translational research. In addition to incorporating its results into the services it offers, it will present its work at national conferences and will publish its findings.

The CTSI DBE activities will **transform** the way in which clinical and translational research studies are conducted at the University of Pittsburgh. By bringing together multiple groups who are working in methodology, epidemiology, biostatistics, and clinical research ethics, investigators can learn from each other. By discussing and working on investigative teams together, the DBE will be able to complement expertise of its faculty. By developing a method to link the most appropriate resource with each investigative team, the DBE will facilitate the best practices in clinical and translational research. In addition, the DBE will enable each investigative team to select and use the most accurate design, the best analytical methods, and the most ethically sound approaches to conducting its research. The investigative team will naturally expand to incorporate other experts as the need arises.

The CTSI believes the efforts of the DBE to develop an innovative and creative new program will advance the science of clinical and translational research at the University of Pittsburgh. By disseminating the results of the DBE Core at national conferences and in publications, those efforts will also advance the discipline of clinical and translational research at the national level.



***Transformation of the Scientist***  
**CTSI Pilot and Collaborative Translational and Clinical Studies**

As new technologies are developed, their inclusion into both basic and clinical research is often stymied by the lack of opportunity for a scientist or clinician to develop the skills necessary to take advantage of a given technique. Similarly, there are relatively few opportunities for an investigator to bring established techniques into his or her research program, if he or she is not already versed in those techniques. Further, excessive demands on their time often preclude clinical scientists and clinicians from even knowing about some new technologies. In times of tight research budgets, the probability of gaining funding for high risk, albeit high payoff, research is diminished, and the negative impact on complex, multi- (or inter-) disciplinary research is particularly strong. Additionally, with the competing demands of the academic setting, it can be quite difficult to bring investigators from disparate disciplines together for constructive dialogue that may generate non-conventional, but potentially breakthrough, ideas. Thus, in order to enhance the development of both clinical and translational researchers, the **specific aim** of this section of the University of Pittsburgh's application for the Clinical and Translational Science Award is to develop opportunities for pilot funding that

1. allow exploration of new technologies, both in an absolute, temporal sense and in the sense of being new to a given investigator, that underpin translational research;
2. allow for exploration of creative multi- or interdisciplinary efforts;
3. engage community health professionals in clinical research; and
4. allow team building and utilization of existing clinical resources and services.

Incorporated into these funding opportunities will be appropriate educational activities. While emphasis will be placed on addressing the training needs of junior investigators, opportunities to engage more senior investigators in integrative and/or innovative studies will also be created.

**BACKGROUND**

The concept of a pilot study is ambiguous, with no common understanding as to what is meant by the term. Per Stewart, a pilot study "is a small preparatory investigation that is in no way intended to directly investigate or test the research hypothesis of interest."<sup>1</sup> Specifically, Stewart indicates that a pilot study is designed (i) to answer the question "Is a trial/experiment worth pursuing?"; (ii) to provide details on how the decision of pursuing an experiment will be made; (iii) to justify the number of animals or human subjects required in a full study and establish statistical estimates for valid power calculations; (iv) to learn how to do a new procedure; or (v) to estimate the time and or cost of a full study<sup>1</sup> Similarly, Polit and Tatano state that the "purpose of a pilot study is not so much to test research hypotheses, but rather to test protocols, data collection instruments, sample recruitment strategies, and other aspects of a study in preparation for a larger study."<sup>2</sup>

In contrast, as noted again by Stewart, the Organization for Autism Research defines a pilot study as "an initial or preliminary investigation designed to test research hypotheses, gather data, and validate the scientific approach and methodology for a particular area of research interest. It is important as a test bed for ideas and as an evaluation and assessment measure before investing further in a major study. Especially for new and up and coming investigators, pilot studies are vital stepping-stones to more significant grants."<sup>3</sup>

The National Institutes of Health has no unique definition for pilot studies, as illustrated by the following statements found in various program announcements or requests for applications:

EXPLORATORY/DEVELOPMENTAL RESEARCH: FEASIBILITY PILOT STUDIES; RELEASE DATE: March 21, 2002; PA NUMBER: PAR-02-088

The NIDCD invites applications for innovative, initial feasibility pilot studies focused on hearing, balance, smell, taste, voice, speech, and language, the scientific mission areas of the NIDCD. *The proposed research should involve the testing of novel hypotheses* or the application of new techniques or methodologies at an early stage of development [Italics added].

PILOT STUDIES FOR CLINICAL TRIALS IN NEUROLOGICAL DISORDERS; Release Date: July 25, 2001; PA NUMBER: PAR-01-119

The NINDS is committed to identifying effective treatments for neurological disorders by supporting well-executed clinical trials. Before proceeding to a full-scale clinical trial, pilot clinical studies are often required. The NINDS announces its interest in supporting pilot studies required to obtain necessary information to clearly establish the clinical basis for proceeding to a full-scale trial. The purpose of PILOT STUDIES FOR CLINICAL TRIALS IN NEUROLOGICAL DISORDERS grant (for brevity referred to as NINDS Pilot Studies grant) is to obtain preliminary data and conduct studies to support the rationale for a subsequent full-scale clinical trial of an intervention to treat or prevent neurological disease ... Examples of relevant research include, but are not limited to, the following: 1. Studies to refine the intervention strategy (dosage, duration, delivery system); 2. Studies to define and refine the target population; 3. Collection of preliminary data for establishing measures of efficacy and safety.

Whether they be called pilot studies or small-scale studies, there is a clear need for enhanced opportunities to conduct research that tests new hypotheses, that enables an investigator to learn additional techniques, that exploits new technology, and that builds multi- or interdisciplinary research teams, as well as for opportunities that allow investigators to define requirements for full scale studies. While important for senior investigators, these opportunities are critical to the career development of junior investigators. Fulfilling this need is a critical step in meeting the NIH Roadmap themes of *New Pathways to Discovery*, *Research Teams of the Future*, and *Re-engineering the Clinical Research Enterprise*.

Even if, or when, opportunities for pilot studies exist, many barriers preclude their full utilization. In particular, barriers to communication and collaboration inhibit potentially transformative research. For the basic scientist, few opportunities to interact with clinical scientists present themselves, even in an academic setting. Thus, the potential to understand his or her work in a broader context, in particular with enhanced clinical insight, is minimized. Although complicated by protective regulations such as HIPAA, clear pathways that facilitate the entry of basic scientist into the clinical world are sorely needed. In parallel, the busy clinician rarely has time to think about the mechanisms that underlie a given disease or syndrome. Even more daunting is finding the time and opportunity to work with the basic scientist to extrapolate from a first step in a disease process to the eventual postulation of potential pathways that lead to disease manifestation. How often does the clinician have time to carefully consider or reflect that his or her clinical observation contains important information about a disease mechanism, a mechanism that, if better understood, could lead to enhanced treatment?

Barriers in communication are not unique to the interaction between clinical scientists and basic scientists. Too often, it is forgotten or ignored that physicians make up only a small percentage of the population of clinical investigators. Nurses, pharmacists, dentists, and therapists who specialize in both physical and mental disorders significantly contribute to the health-related research enterprise. Each of these professions brings a unique – but not complete – perspective to the care of a given patient. How much better could care be if these perspectives were combined into a more holistic approach? This need for broad perspective also applies to research, not only to clinical care. Thus, enhanced mechanisms that bring together the broader community of clinical research professionals are highly warranted.

Barriers to collaboration are not limited to communication issues and have much in common with barriers that hinder an investigator – basic, translational, or clinical – from learning new methodologies. In the traditional academic mold, one's success is measured in “countable” units – the number of papers published, the number of grants received, etc. There is no defined metric for the contribution of ideas to a complex process. It is important to note, for example, that the Federal Government, both through efforts of the NIH and more broadly through efforts of the Office of Science and Technology Policy, is only now beginning to struggle with the concept of crediting more than one “principal investigator” on federal grants. What, then, is the incentive for an investigator to reach beyond his or her acknowledged area of expertise?

## **Existing Pilot Studies Programs and Resources within the University of Pittsburgh Academic Health Center**

### Competitive Medical Research Fund

Since 1985, researchers in the University of Pittsburgh Schools of the Health Sciences have had the opportunity to apply for grants of \$25,000 to support pilot studies that test hypotheses and/or that provide preliminary data needed to support applications for more extensive funding. The University of Pittsburgh Medical Center

(UPMC) Health System established an endowed fund, the Competitive Medical Research Fund (CMRF), to provide modest research support through small, competitive grants made to scientists across the broad range of biomedical sciences represented by the six Schools of the Health Sciences. Depending on the investment portfolio in a given year, total annual funding for awards has ranged from \$\_\_\_\_ - \$\_\_\_\_, with the lower amounts being available in the past two years. The UPMC Board of Trustees remains very supportive of the CMRF, and it has expressed the hope that the investment returns will increase sufficiently that the annual level of funding will return to the \$\_\_\_\_ level. When the number of highly ranked applications, as determined by peer review, has exceeded the number for which funding has been available, the Senior Vice Chancellor for the Health Sciences has provided funding for one or two additional awards, as appropriate.

The University of Pittsburgh, Office of Research, Health Sciences (OORHS), under the direction of the Associate Vice Chancellor for Basic Biomedical Research, Michelle S. Broido, PhD, manages this grant program for UPMC. OORHS issues the solicitation for grant applications, receives the grant applications, reviews them internally for adherence to the CMRF guidelines, establishes peer review panels, conducts the review, analyzes the review results, and recommends funding to the Board of Trustees of UPMC. Thus, for any new opportunity in pilot funding that is sponsored under the CTSI, there is already in place a robust mechanism for administering it.

CMRF grants are awarded in one of three categories:

- *New Investigator awards* are intended to provide funds for relatively junior, independent scientists to develop hypotheses, preliminary data, and methods that will enable submission of highly competitive applications to extramural funding sources.
- *Collaborative Research awards* are intended to fund interdisciplinary, translational research that represents a true collaboration between a clinical scientist and a basic research scientist.
- *Bridge awards* are intended to provide support for investigators who have experienced lapses in funding; *i.e.*, to provide funds to investigators who have applied for renewals of previously awarded grants, but whose renewal grant applications, while receiving highly favorable reviews, were not funded. These CMRF funds are intended to allow concerns expressed through peer review to be addressed.

The two categories most relevant to the CTSI are the New Investigator and Collaborative Research awards.

The most important review criteria for all application categories are scientific merit, health or biomedical relevance, need for funding, and the potential for subsequent peer-reviewed major grant support. Where applicable, the potential clinical impact of the studies is also an important review criterion. Reviewers also evaluate applications for grantsmanship and completeness. Should the reviewer(s) determine that an application and/or supporting materials are not sufficiently comprehensive to allow for adequate review, the application is not reviewed favorably. Poor grantsmanship may, and often does, diminish reviewers' enthusiasm for an otherwise meritorious application.

For the New Investigator category, independence of the junior faculty member is a key review criterion. If the CMRF application is for research that is an extension of an ongoing project (for which either the applicant or someone else is the principal investigator), the applicant must indicate how the proposed project is different from the ongoing project. In addition, if the applicant works in the laboratory of a senior investigator, he or she must clearly indicate how funding will be used for an independent research program and not merely to fund the project or personnel of the senior investigator. It is incumbent upon the applicant to convince the reviewers that the research differs significantly from that of the senior investigator. A letter from the department chairperson demonstrating departmental commitment to the career development of the applicant must be included with New Investigator applications, and demonstration of this commitment is one of the criteria used in evaluating the application. The CMRF applications are often the first competitive application submitted by new investigators, so the inclusion of grantsmanship in the review criteria provides a valuable learning experience to the new investigator. Written reviews are provided to the applicants subsequent to the meetings of the peer review panels, providing valuable feedback as to both scientific questions and issues and suggestions for improved clarity in application preparation.

For the Collaborative Research category, key review criteria include whether or not the work proposed is a true collaboration between a clinical scientist and a basic scientist and the degree to which the proposed work represents immediate or future translation of a research project from the laboratory into clinical practice. That

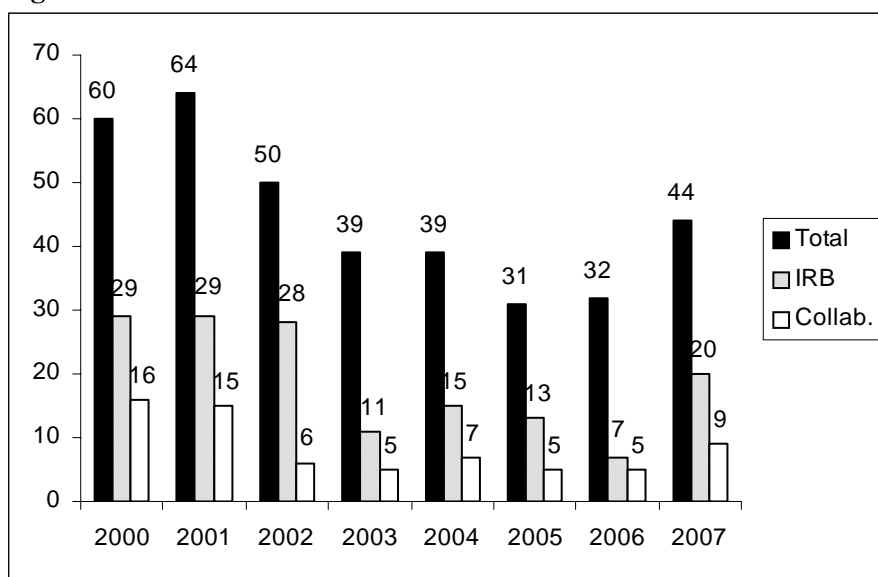
is, the focus of these applications is bench to bedside research. As an aside, it is worth noting that some, although relatively few, of the clinical applications that are received in the new investigator category do have community partners. For applications in which the investigator responsible for the clinical research is not a physician, his or her clinical role must be clearly defined. In addition, the application must demonstrate how the combined efforts in basic and clinical research will result in a collaborative, multi-disciplinary project that will facilitate the translation of research findings from the laboratory to the clinic. For the purposes of the CMRF program, collaborative, translational research projects should address one or more of the following areas:

- Etiology, pathogenesis, and mechanisms of disease with potential application to disease prevention and treatment.
- Clinical knowledge, improved diagnosis (including development of new diagnostic methods or devices), and natural history of disease.
- Disease management (including therapeutics aimed at molecular targets) and molecular epidemiology.

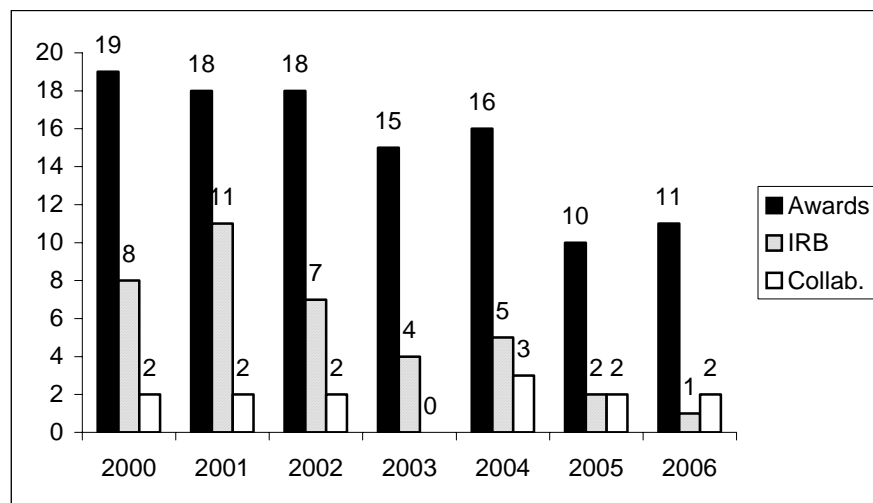
Translation to clinical practice need not necessarily be an immediate consequence of the research performed with CMRF support; however, if this translation will not be imminent upon successful completion of the proposed research, one of the goals of the research should be identification of additional gaps of knowledge that must be filled before such a translation could be made.

Collaborative Research grants have only been awarded for seven years (Fiscal Year 2007 applications have been received but have not yet been reviewed.) During this time, an average of 18% of the CMRF applications received and 12% of the grants awarded have been in this category (Figures 1 and 2). It is important to note that, as part of the application, research teams who have significant other funding must include specific statements to address why CMRF support is needed to perform the proposed research; evaluation of these statements is part of the review process. The majority of applications received to date in the Collaborative Research category have involved at least one senior scientist, and many worthwhile proposals have not been funded because reviewers have not been convinced of the need for CMRF support. *The development of a mechanism to engage more junior researchers in such activity is indicated.*

Over the past eight years, an average of 41% of the applications received (all categories) would have required IRB-approved protocols if awards were to be made (Figure 1). Of the awards actually made over the previous seven years, approximately one third of the awards (all categories) have required an IRB-approved protocol (Figure 2). Again, these are for projects that are hypothesis driven and designed to develop the pilot data necessary to be competitive for more substantial awards. Important in the context of the CTSI, relative to the previous four years, the number of applications received that would require IRB approval before funding increased substantially in the most recent solicitation cycle (Figure 1). This is coincident with the implementation of new efforts by scientific staff members in the Office of Research, Health Sciences to make sure that all new investigators (basic, translational, or clinical) in the six Schools of the Health Sciences are aware of the CMRF program.



**Figure 1:** The total number of applications received in each of the past eight years, and the number of these that required IRB approval or that were submitted under the collaborative category.



**Figure 2:** The total number of applications funded in the previous seven years (FY2007 review has not yet occurred); and the number of these that required IRB approval or that were funded under the collaborative category.

As explicitly stated in the CMRF policies, one of the goals of the program is to provide funds “...to develop the preliminary data and refinement of procedures and hypotheses that would enable submission of highly competitive applications to national funding sources.” The success of this program in achieving this goal is illustrated by the fact that as of May, 2005 ten individuals who received awards in 2002 had received subsequent NIH funding, and six had received research funding from private foundations/associations; no data were available on the other two awardees. By May, 2005 eight of the individuals who had received awards in 2003 had received subsequent NIH funding, and two had received research funding from private foundations/associations; no data were available on the other five awardees.

#### CMRF Genomics

In Fiscal Year 2005, the number of CMRF applications that were highly ranked by peer review was less than the number that could be funded using that year’s allocation of CMRF money. The UPMC Board of Trustees agreed to allow the remaining funds, matched by funds provided by the Senior Vice Chancellor for the Health Sciences, to be used to support a new, one-time program for pilot projects that would use genomics techniques in clinical research. The Pilot Projects Using Genomics Techniques in Clinical Research program (CMRF Genomics) was developed by the Associate Vice Chancellor for Clinical Research (Dr. Reis) and the Associate Vice Chancellor for Basic Biomedical Research (Dr. Broido) in recognition that (1) data obtained using genomics technologies may provide insight into disease mechanisms, risk assessment, diagnosis, and/or treatment; (2) many clinical researchers have not had the opportunity to learn about the application of modern genomics technologies to clinical research; and (3) inclusion of preliminary data is often required for submission of grant applications to external funding agencies and lack of familiarity with genomics technologies precludes the acquisition of such data. The program was directed towards junior clinical researchers (fellows and assistant professors), and it included both a strong educational component and a demonstrated departmental commitment to the proposed research.

The educational component of the CMRF Genomics program included three important aspects. First, two months prior to the application receipt deadline, the Office of Research, Health Sciences and the Office of Clinical Research, Health Sciences co-sponsored a workshop, offered twice, entitled “Genomics for the Clinician.” Each offering of the workshop involved presentations by physician-scientists who had conducted clinical research studies that involved the collection and analysis of genomic data and that demonstrated the clinical importance of such data. Also included in the workshop program were overview presentations of the genomics technologies available in the Genomics Core Laboratory and a description of their utility for obtaining data important for clinical studies. Potential applicants were strongly encouraged to attend one of these workshop sessions. Second, as part of the application process, the principal investigator was required to meet with the Director of the Genomics Core Laboratory to determine the most appropriate technology for

answering his/her clinical question and to assess the feasibility of the project. Third, if an award was made, the principal investigator was required to work closely with the technical staff of the Genomics Core on sample preparation, data acquisition, and data analysis.

As a component of the CMRF Genomics application, applicants were required to provide evidence of strong departmental commitment to the proposed research. This requirement was based on the fact that the junior clinicians' time is often over taxed and resources for independent research are limited. For example, although many assistant professors at the University of Pittsburgh School of Medicine are hired with an expectation that 25% of their effort will be devoted to clinical responsibilities and the remainder towards research, several others are hired with a greater percentage of their effort devoted to clinical care but who are nevertheless expected to develop research programs. Further, clinical fellows rarely have the opportunity to develop a research project for which they have primary responsibility. Thus, CMRF Genomics required a financial commitment from the applicant's home department to the proposed research effort. Based on several years of experience, the Director of the Genomics Core Laboratory determined that an award of \$10,000, expended in services at the Core, would be sufficient for a preliminary study of the type solicited under CMRF Genomics. In order to ensure that the junior scholars would have departmental concurrence that the proposed studies would be a valuable component in the development of the junior clinician-scientist's research career, the home department of the applicant was required to provide \$2,500 in matching monies to the \$7,500 provided by the program. Additionally, as part of the application, a letter of support from the applicant's mentor or from the relevant division chief or department chairperson had to be included. In addition to explicitly acknowledging that monies provided under this grant program would be awarded directly to the Genomics Core Laboratory, this letter had to identify the resources available to the applicant for the proposed work, including the availability of the relevant patient population, the source of any biological samples to be used in the study, and any logistical support necessary for the performance of the research.

The application was simple, requiring no more than five single-sided pages to present a discussion of the clinical problem/question that would be addressed by the proposed study; a description of the source of tissue, DNA, or other clinical material to be used; and a description of the research to be performed. Applicants were expected to describe how the study would address the clinical question being posed, identify the genomic technique to be used, indicate why the technique is the most appropriate to answer the question, describe how results would be analyzed, and provide an explicit statement as to how the research would enable more in-depth studies. Review criteria were straightforward: is this an important clinical question? is the project feasible? is there potential for this pilot study to lead to more comprehensive studies?

Six eligible applications were received, and five awards were made. All applications were from faculty members. It is reasonable to speculate that the time constraints placed on fellows was too great to allow them to participate in the grant program. Although the number of applications was relatively low when compared to other institutional grant solicitations, it must be noted that proposals for this RFA necessitated access to large clinical populations in which it is feasible to collect DNA. It is also important to note that the value of the program extended beyond the numerical count of the number of awards made. In particular, the value of the workshops transcended the direct value to those clinician scientists who submitted applications to the CMRF Genomics program. These two workshops were attended by a total of 95 people. Whether or not individuals were in the position to respond to the CMRF Genomics solicitation, an important educational experience was provided to clinicians representing 18 medical specialties, as well as for investigators with primary interests in nursing, pharmacy, and public health. Whether or not these scientists incorporate genomics into their immediate research activities, they have gained awareness of the power and potential of these technologies and of the services offered at the University of Pittsburgh. Because the pilot studies are still ongoing, it is not yet possible to determine the impact of these projects on post-study research activities.

#### Other pilot/small grant opportunities

In addition to the CMRF program, funded through a UPMC endowment, funds for pilot programs are also made available to University of Pittsburgh investigators through other institutional resources, NIH grants, and public and private foundations. Examples of these programs follow.

The University of Pittsburgh, through the University Research Council, administers an annual small grants program that provides seed funding to develop ideas to the point where external funding can be obtained and/or to support research in areas where external funding is extremely limited. Although faculty members

with primary appointments in the School of Medicine are not eligible to apply for this program, faculty from the other five Schools of the Health Sciences may apply. Awards range from \$2,000 to \$16,000. Another institutionally administered opportunity for pilot funding is provided by the Office of Technology Management, which offers small grants for pre-commercialization activities and prototype development to advance faculty inventions that are too rudimentary for licensing. Funds for this program are provided by institutional, private, and state resources. The Magnetic Resonance Research Center and the Positron Emission Tomography Facility jointly sponsor the Pilot Imaging Program which is designed to stimulate and support new research directions. With monthly receipt dates for submission of five page pilot imaging applications, the goal of this program is to allow researchers at the University to obtain sufficient preliminary, hypothesis-driven data (MR or PET) to enable a competitive application for externally funded research. Typically, three - four PET pilot imaging studies are supported each year, and six MR studies are supported.

The Children's Hospital of Pittsburgh Scientific Program, established by Children's Hospital of Pittsburgh (CHP) and UPMC, launched an Innovation Awards Program this year. This pilot grants program is designed to stimulate basic and clinical pediatric research that is highly innovative but unlikely to garner NIH funding without preliminary data. Applicants can request up to \$\_\_\_\_\_ per year for two years for projects that are not yet supported by extensive preliminary results, have the potential to open new areas for investigation, or have a high likelihood of changing clinical practice. Several criteria are considered upon review by a panel made up of an internal advisory board and one or two invited reviewers. The most important of these criteria are the proposal's degree of innovation, its potential impact, and inclusion of multidisciplinary collaborative strategies. Proposals that include collaborative efforts among CHP pediatric researchers and investigators from departments, institutes, or centers within the School of Medicine and UPMC will be viewed favorably. A total of \$\_\_\_\_\_ is available for funding in the first year and \$\_\_\_\_\_ is expected to be available in each subsequent year.

Several active NIH grants to the University include, as part of their funded activities, support for "seed" or "pilot" studies. These studies are typically funded in the range of \$20,000 – 50,000 for a one year period. Illustrative of the NIH funded grants that support pilot studies are the *Rheumatic Disease Core Center* (P30, NIAMS); *Mitochondrial Targeting Against Radiation Damage* (U19, NIAID); *SPORE in Head and Neck Cancer* (P50, NCI); *SPORE in Lung Cancer* (P50, NCI); *Cancer Center Support* (P30, NCI); *Pittsburgh Older American Independence Center* (P30, NIA), *General Clinical Research Center* (MO1, NCRR), among others.

Private foundations have also made monies available for pilot projects. The David Scaife Foundation, as part of the award used to establish the Pittsburgh Institute for Neurodegenerative Diseases at the University of Pittsburgh, included funds to support "Seed Money Grants for Research Related to Neurodegeneration and Stroke." The Shadyside Hospital Foundation provides pilot funds for patient-centered research that enhances patient care, community outreach, and services to the disadvantage.

Investigators at the University are notified of the availability of these diverse funding opportunities through various mechanisms. In most cases, the Office of Research, Health Sciences is informed of pilot funding opportunities, and these are subsequently posted on the OORHS website, on a page specifically dedicated to "Targeted Pilot Funding." In addition, those opportunities which are specifically cancer-related are disseminated by the University of Pittsburgh Cancer Institute to its broad membership. The few opportunities that are not brought to the attention of OORHS are not showcased on its website. Additionally, it is not clear how effective this mechanism is for disseminating the information to a wide audience. Nevertheless, these pilot project programs are attracting both clinical and basic investigators. Note, for example, that of the six applications funded in Fiscal Year 2005 for the SPORE in Head and Neck Cancer program, four required IRB approval. Similarly, four of the six applications funded by the SPORE in Lung Cancer in 2005 required IRB approval. Of the 26 applications received in the past five years for the pilot program sponsored by the Alzheimer's Disease Research Center, 11 required IRB approval; of the ten awards made during this period, four required IRB approval. In addition, 95% of the proposals received and 100% of those funded by the University of Pittsburgh Claude D. Pepper Older Americans Independence Center Pilot Grants Program in the past two years have required IRB approval.

The pilot project programs discussed here are illustrative of the programs that are specifically available to University of Pittsburgh faculty members. There are, of course, a wide range of nationally competitive pilot

programs, supported by the federal government, industry, and foundations, to which University faculty routinely apply.

## **CTSI PILOT AND COLLABORATIVE TRANSLATIONAL AND CLINICAL STUDIES CORE: DESIGN AND METHODS**

### Enhancing Existing Programs:

As noted above, several existing programs within the University of Pittsburgh Academic Health Center provide opportunity for clinical and translational investigators to engage in pilot studies. However, several of these programs would be enhanced by greater visibility and greater outreach to a broader research community, thus expanding the likelihood for innovation and integration. Activities to do so are described below.

*CMRF:* Consistent with the goals of CMRF as established by the University of Pittsburgh Medical Center, the program will remain an investigator initiated program. However, enhancements can be made to increase the participation of clinical investigators and the number of collaborative (translational) projects. With regard to clinical investigators,<sup>1</sup> educational programs will be developed to provide knowledge in basic concepts (*e.g.*, study design), methods (*e.g.*, family-based research), and tools (*e.g.*, informatics) using the existing “Clinical Research Seminar Series” as a framework; (2) CTSI resources will be made available to help develop applications (*e.g.* statistics, study design, and clinical research ethics core), and (3) solicitations will be widely promoted throughout the AHC campus through initiatives of the CTSI Center for Clinical and Translational Informatics and through the CTSI Education, Research and Career Development Core. With regard to increasing the number of collaborative projects, see below.

*Grant funded pilot project opportunities:* The OORHS website includes a searchable database of available grant application submissions, ranging from federal to foundation supported to internally supported solicitations. Specifically, it is possible to search this database for opportunities focused on “targeted pilot studies” (supported by the full range of funding sources). No data are currently available as to the frequency with which this search is performed. An initial step toward increasing the number of participants in pilot research studies is to enhance the completeness of the OORHS website as a central repository for information about such opportunities. While most faculty members who manage a pilot program are diligent about sharing notices with OORHS, some faculty are not aware of the services that OORHS provides. Historically, pilot opportunities that have not been brought to the attention of OORHS staff have been posted on the calendar of University of Pittsburgh Health Sciences (web) Portal (<http://calendar.health.pitt.edu/>). OORHS staff will work with the individuals who manage the calendar to ensure that all relevant information is shared with OORHS. Further, the CTSI website will contain a prominent, explicit statement that information about funding opportunities for pilot projects should be brought to the attention of OORHS.

A second step is to ensure that eligible investigators are made aware of such opportunities. Thus, in addition to continuing to post opportunities on the OORHS website, a prominent link on the CTSI website will direct investigators to the OORHS “targeted pilot funding” webpage. Further, e-mail notification of these opportunities will be sent to investigators who have submitted IRB applications using the newly implemented IRB submission process (OSIRIS).

A third step to increase the number of applicants for pilot research funds is to raise general awareness of the most relevant scientific/clinical questions in a given research area. In this awareness lies the opportunity for transforming the scientific approach to a given clinical field. Specifically, the ultimate impact of pilot programs is enhanced if the participants come from a broader spectrum of scientists than those who are already working in the field. Individuals who are naïve to a given scientific problem may be able to provide valuable insights from varied perspectives, yet, to be able to do so they need to be made aware of the key questions or observations for which new understanding is needed. Thus, if there is to be broad outreach to bring “new” (not necessarily junior) investigators into a disease specific area, a mechanism to provide education in at least some of the seminal questions of a given field is required. To facilitate this awareness, each solicitation for pilot research projects that comes from a source managed by University investigators (*e.g.*, SPORE grants or internal funds) will be accompanied by a web-based tutorial detailing some of the key, outstanding questions in that field. By way of example of the elements that might be contained in such a web-based tutorial, the announcement for the 2006 “University of Pittsburgh Head & Neck Cancer SPORE Developmental Research



(Pilot Project) Program” states that “[a]reas of interest include, but are not limited to, cell biology, genetics, immunology, molecular carcinogenesis, epidemiology ...” A web-based tutorial would include a description of head and neck squamous cell carcinoma including the incidence and known epidemiologic factors that contribute to the disease (*e.g.*, exposure to tobacco and alcohol). The current prevention, diagnostic and treatment strategies would be discussed with a focus on areas where further investigation is most critical. In addition, a brief description of the SPORE Cores and projects would be presented as well as the other scientific activities in the head and neck cancer program with links to the webpages of the investigators. Of course, no such tutorial can be complete, and efforts will be taken not to imply that the questions identified are, in and of themselves, complete.

#### New opportunities:

In canvassing University of Pittsburgh faculty members as to why they do not become more actively involved in research that involves a partnership between basic scientists and clinical scientists, the most frequent response is “time.” There is growing interest on the part of both basic scientists and clinical scientists in speaking to each other, but the temporal demands of their jobs, particularly for clinicians, is such that the opportunities to sit down and engage in scientific dialogue are rare. As noted by several University clinicians, the best time of the day for them to attend meetings is between 6:00 am and 8:00 am; this is a time period during which most basic scientists are just beginning to stir. Similarly, clinicians can rarely take time during the middle of the day to attend a seminar, no matter how interesting the subject may be to them, while basic scientists are able to plan their days around robust seminar schedules. In an ideal world, a physical venue – a meeting place, a lunch room, a tea room – shared by scientists who cover the spectrum of research interests from basic to translational to clinical is critical to maximize constructive interactions. However, a physical venue does not solve the temporal disconnect. Thus, under the CTSI, there will be a virtual venue for interaction, one that can be accessed electronically which inherently has no temporal constraints.

What is the intent of this virtual venue? This is perhaps best answered by example. A basic scientist makes an observation that she believes may have clinical relevance, but the molecular or cellular system on which she is working may have relevance to a spectrum of medical functions, diseased or normal. With whom does she discuss her observation? What she wants is to be able to say to clinicians of different specialties that she has made this observation and that she wants to know if it correlates with anything seen clinically. Similarly, a clinician may make an observation that a certain protein is abundant in two very different disease states, but he may have no inkling as to why this may be the case. He would like to know more about the protein function under a variety of conditions and more about the family of proteins of which it is a member; he may need to speak with different basic scientists who each can bring a piece, but a only a piece, of the puzzle together. This virtual venue is thus a forum in which these investigators can throw out open-ended questions, seeking responses from colleagues without having to know in advance either the name of the specific colleague or even the field of expertise that may be most relevant. Thus, this virtual venue is complementary to the tools to be provided by the CTSI Online Research Community.

Because of the rapidity of change and development in electronic communications, it is not possible to specify at this time the exact nature of the virtual venue, but it is anticipated that it will be something that merges assets of a blog, a chatroom, and a virtual library of the type supported by Bioinformatics.org<sup>4</sup> The CTSI Center for Clinical and Translational Informatics will develop and support a platform for the following concept, a CTSI-log. An investigator who would like to initiate a discussion about a research question or a research observation would post free form text; this text could be supplemented by links to related published articles or abstracts. The initiating investigator would also be able to create a category that would be used as a search mechanism by other investigators who would be browsing or searching the site. For example, a category could be as specific as “Adrenomedulin as a clinical mediator? Relevance of structural studies” to a general question such as “Why is loss of smell identified as a symptom of Parkinson’s Disease (PD) only after a PD diagnosis” to a general research topic of “Proteins involved in EGF receptor trafficking.” The browsing investigator whose interest is captured by an entry could respond with comments as part of the ongoing posting to the site. Another possibility is “chat space” for real time dialogue between interested parties. Access to these sites would be restricted to members of the University of Pittsburgh and UPMC communities; this will lessen concerns about being scooped or of rival investigators having access to unpublished data.

What is the likelihood that such a forum will be used effectively? Some general statistics about the demographics of internet use for work-related purposes are somewhat informative in predicting the utility of a

CTSI-log. Although a December 2005 survey reported that only 4.4% of blog users are between the ages of 30 and 39 and only 1.4% are of age 40 or older<sup>5</sup>, a 2004 report found that “older Baby Boomer Internet users (between 50-58 years old)” are similar to “Generation X Internet users (between 28 and 39 years old)” in that “59% of Generation X Internet users and 55% of Baby Boomer Internet users do research online for their job ...”<sup>6</sup> Further, a “News Feature” column in the December 1, 2005 issue of *Nature* discusses the use of web tools for communicating ideas, questions, and results<sup>7</sup>. While, in general, web based tools such as blogs are not widely used by scientists, the column quotes an Associate Professor of Biology at the University of Minnesota Morris, Paul Myers, who, in reference to posting scientific results on a blog, states that “People who are very far afield from your usual circle start thinking about the subject. They bring up interesting perspectives.”<sup>7</sup> Supporting the idea of promoting targeted discussion among scientists from disparate backgrounds, scientific publishers including the American Association for the Advancement of Science, the Nature Publishing Group, and the Oxford University Press have established focused science blogs<sup>8</sup>. Thus, while it may be junior investigators who take advantage of CTSI-log initially, the rapidly increasing use of IT tools, as discussed elsewhere, by physicians, physician scientists, and basic scientists at the University of Pittsburgh bodes well for the long term success of CTSI-log. It is also worth noting that the use of electronic media for scientific discussions is gaining a foothold at the NIH. In a discussion of changes to be made in the NIH review process, Dr. Antonio Scarpa, Director, Center for Scientific Review, states that CSR is “...experimenting with new electronic technologies that permit reviewers to have discussions with greater convenience and to spend less of their precious time in traveling. For example, asynchronous Internet-assisted discussions – secure chat rooms – allow reviewers to ‘meet’ and to comment independently of time as well as place.”<sup>9</sup>

If successful, such a virtual forum for dialogue [CTSI-log] will lead to the development of new, potential collaborations that are inherently multi- or interdisciplinary in nature. Such potential collaborations will need to be cemented through pilot studies. While the opportunity for such collaborative studies is available through CMRF, CMRF currently has a single annual receipt date for applications. **CTSI will augment the CMRF program by inviting collaborative research applications on a quarterly basis; at least \$\_\_\_\_\_ will be made available on an annual basis for such studies.** Solicitations for these awards will be made through mechanisms similar to those used for the already established CMRF program, including website postings, faculty e-mailings, and orientation meetings with junior faculty. Similarly, review criteria and the review process will parallel those for the CMRF collaborative award as described in the preliminary studies section above.

New opportunities provided through the CTSI will be tailored to specific areas or technologies and will be targeted towards clinical investigators to allow them to “... test protocols, data collection instruments, sample recruitment strategies, and other aspects of a study in preparation for a larger study.” The general paradigm of the CMRF Genomics program will be followed. Specifically, an educational activity will be organized to accompany the solicitation and, when appropriate, some level of matching funds will be requested to ensure that the applicant is supported by his/her department in the proposed research endeavors. The criteria for review will also be similar to the CMRF Genomics program, as described above. Funding provided through the CTSI will range from \$\_\_\_\_ - \$\_\_\_\_. The selection of topics for these solicitations will be coordinated with the CTSI Executive Committee. In particular, focused efforts will be made to promote wide exposure of those technologies that the Executive Committee sees as essential for building bridges between basic and clinical investigators, especially those that may be components in the integrating and innovating activities that may be supported under the Novel Clinical and Translational Methodologies section of this application. In recognition, however, that significant innovative research activity conducted under more local or individual auspices will continue, targeted solicitations that focus on technologies that do not fall immediately under the integrating rubric may be issued.

*Examples of Targeted Pilot Programs that may be conducted under the CTSI:*

PET and MR Imaging provide a comprehensive example of the range of activities potentially supported under the CTSI. As noted above, an internally funded Pilot Imaging Program (PIP) is already in existence, the goal of which is to generate imaging data that will enable competitive applications for external funding. The scientists who manage this program, Drs. Chester Mathis and Fernando Boada and Ms. Denise Davis, are eager to promote increased use of PET and MR technologies by investigators across campus, both for brain imaging and for “body” imaging. They have agreed to conduct targeted workshops, à la CMRF Genomics, that they feel would be extremely valuable in educating both junior and senior investigators about the potential of imaging studies in addressing key scientific questions. Further, while the PIP supports hypothesis driven studies, there

is a modest amount of time available on the relevant imagers to support studies whose purpose is to (i) provide an investigator with the opportunity to learn about a new, critical technology, and/or (ii) to define the requirements for future, hypothesis driven studies. Typical costs associated with these imaging preliminary study projects, to be provided by the CTSI, would range from \$ \_\_\_\_ (for MRI) to \$ \_\_\_\_ (for PET).

While mass spectrometry has long been a mainstay of chemical research, its utility in biomedical research is only now burgeoning. Whether for basic, translational, or clinical application, mass spectrometry has recently become a mainstay of proteomics research. However, the utility of mass spectrometry in biomedical research is not limited to proteomics. For example, Dr. Samuel Poloyac, a pharmacist and PhD scientist in the School of Pharmacy, is actively collaborating with investigators from the School of Nursing and from the School of Medicine on projects that involve the use of mass spectrometry for monitoring small molecule metabolites as biomarkers of insult or as potential therapeutic agents. Complementing his own studies in animal models, he is collaborating with investigators in the School of Nursing to explore the hypothesis that the presence of a specific hydroxyeicosatetraenoic acid (20-HETE) in the cerebral spinal fluid of patients who suffer hemorrhagic strokes is associated with the development of cerebral vasospasm during the clinical course. Supporting animal model data suggest that there may be potential therapeutic utility in affecting the formation of 20-HETE after stroke. He is also working with collaborators at the Safar Center for Resuscitation Research in the School of Medicine on designing clinical studies that will explore the clinical implications of altered cytochrome P450 metabolism in patients receiving therapeutic hypothermia after cardiac arrest. The major tool that is used in monitoring these metabolites is mass spectrometry. Dr. Poloyac is a committed translational investigator and educator, and he is eager both to provide workshops on the use of mass spectrometry for monitoring small molecule biomarkers/metabolites in clinical samples. He is also committed to providing his expertise and the collaborative use of his mass spectrometers for pilot studies in this area.

Traditional optical imaging methods for the diagnosis of human disease commonly rely on static histopathologic images or low resolution images of tissues; they are time consuming, difficult to standardize, generally demand surgical biopsy, and can be unreliable for diagnosis. However, over the past several years, microscopy as a scientific tool has evolved from a small group of principally descriptive methodologies to a wide range of tools and techniques that allow investigation of dynamic processes as well as the molecular organization of organs, tissues, and cells. Advances in microscope and camera design, fluorescent dye technology, the development of fluorescent proteins, as well as the advent of inexpensive powerful computers, have made simultaneous resolution and quantification of multiple concurrent molecular markers at a sub-micron resolution a reality. The development of confocal microscopy has allowed optical sectioning and reconstruction of tissues in three dimensions. Finally, the development of multiphoton methodologies as an extension of optical sectioning microscopy has further improved the potential utility of these methodologies when examining living or light scattering tissues. Dr. Simon Watkins of the University of Pittsburgh Center for Biologic Imaging (CBI) has been collaborating with Optiscan, an Australian company that has developed fiber optic confocal microscopy for conducting miniaturized *in vivo* imaging. The CBI has a prototype device available to its research team and is using fiber optic delivery and collection to develop examples of *in vivo* confocal imaging applications. These applications include imaging the microvasculature of rat gingiva and skin, examining the cellular and microvascular structure of hairless mouse skin, imaging the microvasculature and nerves in rat vas deferens and colon, observing melanoma and rat colonic mucosal structure, assessing burns, and tracking subcellular localization of transdermally applied oligonucleotides in human skin grafted onto mice. These latter data show the potential utility of the confocal microscope to image sections at several depths within the skin. Translational and clinical extensions of these animal studies will offer many opportunities for pilot studies to apply *in vivo* confocal imaging for detection, diagnosis, therapy, and tracking delivery of therapeutic agents to various human diseases and injuries. Dr. Watkins has collaborated extensively with clinicians on various research projects. He is committed to training individuals in modern microscopic techniques and eager to participate in the development of an educational workshop and confocal imaging pilot program as part of a CTSI.

The preceding three examples develop opportunities to allow investigators to gain experience with techniques that are new to them but that are not new in terms of technological development. In concert with the Office of the Senior Vice Chancellor for the Health Sciences, the CTSI will develop opportunities to bring new – in the temporal sense – technologies to investigators in the health sciences. For example, with the growing recognition of the importance of microRNA molecules in gene regulation and the implications for cancer and developmental disorders has come the desire on the part of University investigators to incorporate microRNA

technology into their research activities.<sup>10, 11</sup> With the support of the Senior Vice Chancellor for the Health Sciences, the Office of Research, Health Sciences is working with the Genomics Core Laboratory to develop a capability in microRNA technology that includes on-site expertise. A pilot project program that focuses on microRNA studies is the quintessential way to share that expertise broadly.

The opportunities to participate in pilot projects are an integral part of the CTSI. The power of searching complex biomedical data using the system known as Diamond<sup>12</sup> is described elsewhere in this application (see Novel Clinical and Translational Research Methodologies Core). Pilot projects that exploit Diamond's capabilities will be provided under the CTSI.

It is anticipated that at least the initial set of opportunities for pilot funding will focus on topics and technologies particularly germane to bench to bedside translational studies and clinical research; however, pilot programs that have the potential to enhance interactions between community health professionals and University investigators will be critical for taking findings from the bedside to the community. Definition and development of such activities will require direct input from the proposed group of participating practitioners. By way of example, in conversation with a physical therapist in private practice who is also the president of the local physical therapist association, the Associate Vice Chancellor for Clinical Research, Dr. Reis, discussed the concept of the CTSI helping to provide an educational program for physical therapist that would be focused on evidence based practice. The physical therapist agreed that such a program could successfully educate the new trainees who will eventually change the standard of practice, but she also expressed concern that established health professionals would be reluctant to make changes in their practice. She stated that, at least in physical therapy, studies that are cited as the basis for "evidence based practice" do not take into account that patients have comorbidities and/or more than one joint or body part that is affected by the disease. Therefore, many of the studies are not necessarily applicable to the whole patient seen in private practice settings. In addition, she noted that evidence based practice in her field is not uniformly adopted because many of the latest developments are not reimbursed.

One approach to address these concerns is to develop a pilot funding program directed towards a select group of community-based health professionals. This program would offer a modest, but appropriate, level of financial support to conduct small studies in the offices of these professionals, designed to address problems that these practitioners have identified as relevant to their practices. The CTSI would provide additional support such as assistance in study design and analysis, bringing to bear on the study the full and appropriate range of multidisciplinary university investigators with expertise relevant to the project. If successful, such pilot studies will develop bonds between investigators and practitioners, will engage the practitioner in the research process, and will lead to the development of more comprehensive studies that unite university investigators with community professionals in robust research activities.

While not comprehensive, each of the proposed enhancements, tools, and pilot programs described above bring together people from diverse disciplines, whether it be as co-investigators or through the associated educational experiences.

#### Clinical Investigation Team Building Program

The pilot programs proposed here have been designed to develop the translational and clinical research enterprise at the University of Pittsburgh by providing funds for investigators to explore research areas that are either new to them or that require a collaborative effort between clinician scientists and basic scientists. A significant number of participants in these opportunities will be investigators who are new to the University or who are newly independent, and these individuals are not likely to be well versed in the extensive and resource-rich, clinical and translational research environment at the University of Pittsburgh and at UPMC. These individuals are unlikely to know who at the University has similar research interests and goals, where the experts in areas such as biostatistics reside, and how to comply with the regulatory issues associated with conducting clinical research. As a means to integrate these scientists into the clinical and translational research enterprise at the University of Pittsburgh, a CTSI Clinical Investigation Team Building (CITB) Program will be developed. This intensive mentoring program will assist faculty members who are new to the clinical research enterprise at the University to develop their research ideas and to identify investigators who have expertise in relevant, complementary areas. The CITB program will guide new faculty members through the entire process of building a clinical or translational research team and of designing and implementing a clinical study. The program will initially be limited to facilitating studies that are most effectively conducted

using the resources of the Montefiore University Hospital Clinical and Translational Research Center (CTRC, former GCRC site), a setting particularly suited to in-depth translational research that relates sophisticated clinical description to advanced phenotyping and genotyping data. The CTRC is discussed in more detail in the “Participant and Clinical Interactions Resources” section of this application. The CITB program will begin as a small program focused on studies that can be conducted in the CTRC. If successful the program will be expanded to include a broader array of studies.

Investigators who would like to participate in the CITB program will be asked to provide a written proposal of their research plans and goals. Investigators may submit proposals for consideration at any time and the decision to accept a proposal will depend upon whether it has sufficient merit to maintain support as it transitions through a defined series of milestones or phases (Table 1). A Pilot Studies Review Committee will establish specific criteria for selection of proposals.

**Table 1:** Phases of CITB-facilitated clinical or translational project development and implementation

	<b>CITB-facilitated activity</b>	<b>Expected Outcome</b>	<b>Funding Source</b>
<b>Phase I</b>	Team Building	Team of investigators with expertise in and enthusiasm for research topic	CITB Programmatic Service
<b>Phase II</b>	Project Building	Complete, written research proposal for submission to an external funding agency	
<b>Phase III</b>	Project Translation to an IRB approved protocol	IRB approved protocol for conduct of study	
<b>Phase IV</b>	Project Implementation	Subject accrual and data collection	Extramural Agency or CTSI Pilot Program
<b>Phase V</b>	Data Analysis		

The objective of the first phase of the program will be to build an interdisciplinary, collaborative team. The CITB will suggest discipline experts to advise or mentor the investigator on different aspects of the project. CITB staff will coordinate one-on-one meetings between the investigator and the identified discipline experts. Following these meetings, a written critique from the experts and an indication of their enthusiasm for the project will be requested; the investigator will be asked to comment as to whether he/she considers the discipline expert a relevant potential team builder or member. At the conclusion of this process, the CITB will determine whether reciprocal interest among potential team members warrants transition to the project building phase of the program.

During the project building phase, Phase II, the CITB will provide administrative assistance in scheduling meetings among participants, provide access to online communication tools with project-specific collaboration websites, provide project management advice (in regulatory requirements, budget preparation, etc.), assist in tracking drafts of written materials, and assist in the overall process of project development. At the conclusion of Phase II, the product of the collaborative interaction among team members and the CITB will be a complete, written research proposal that is considered appropriate for submission to an extramural funding agency.

Phase III will begin immediately after the proposal has been submitted to an extramural agency for funding. By beginning preparation of the necessary IRB protocols soon after proposal submission, potential delays in project implementation that occur due to incomplete regulatory approvals will be reduced or eliminated. The CITB will assist with the writing of standard operating procedures, informed consent documents, and with the creation of relevant case report forms, data forms, and online study-specific space for study data maintenance. In addition, detailed planning for study subjects advertising, patient recruitment, and study logistics will be completed under Phase III. The final product of Phase III will be a comprehensive protocol with full regulatory approval that is ready for patient accrual to begin.

Optimally, direct funding will be provided to the investigator by an external funding agency. If a proposal is not funded by an external agency, then the reviewer’s comments will be assessed and a determination will be made as to whether the addition of preliminary data, a demonstration of feasibility, or a more complete assessment of variables will make the proposal more competitive. If such is the case, the investigator may submit an application to an appropriate CTSI pilot program. Once funding is available, whether from external or internal sources, CITB contribution to the project will continue through Phase IV and V, Project Implementation and Data Analysis, respectively. If funds for these phases are provide by a pilot program, then the project will be less extensive than proposed in the initial submission to an external agency and will be

specifically directed towards making the application stronger for resubmission to an external agency. CITB contributions during these phases will be those provided by the CTSI core facilities, including support for patient accrual, protocol implementation, biomedical informatics, laboratory tests, modeling, and statistical analysis.

The CITB program will be conducted through the Clinical Investigation Core (CIC) of the CTRC. The CIC staff includes MD's, PhD's, RN's, and IT support technicians. The CIC strives to offer both clinical investigators and basic science investigators a quality translational research management service with expertise tailored to their needs. The CIC offers expert assistance in translation of a research proposal to protocol and consent form preparation for IRB and regulatory requirements. Support is provided by nurse coordinators in patient recruitment. Routine internal audits are conducted to maintain quality control, consistent with "Good Clinical Practices." The CIC has successfully created new collaborative opportunities for clinical investigators from various disciplines including obstetrics, hepatology, pulmonology, geriatrics, and pharmacoepidemiology.

### **Evaluation Plan**

The expected outcomes from implementing these programs include an increased number of clinician applicants and broader representation of research/medical fields in already existing pilot programs, and more interdisciplinary, collaborative efforts among both junior and established basic and clinical scientists. In order to track the success of these new initiatives, traffic on the web-based communication tools, participation in the technology education programs, applicant numbers for each pilot program, and the success of pilot award recipients in obtaining extramural funding will be assessed on a regular basis. For details of the evaluation process please see the CTSI Evaluation and Tracking Plan section of the application.

### **Proposed Timeline for Implementation:**

Year 1	Year 2	Year 3	Year 4	Year 5
Develop CTSI-log	Implement CTS I-log	Track CTSI-log usage; promote awareness and use and modify features, as needed.		
All years: solicit and award collaborative proposals on a quarterly basis				
Solicit and award PET/MRI imaging preliminary study projects			Solicit and award PET/MRI imaging preliminary study projects	
All years: develop pilot grant programs based on identified needs of the CTSI community. Solicit and award grants as programs are developed. The following are examples of the types of programs that may be developed in different years:				
New technology utilization program	Variable-defining/ Instrument-testing pilot program	Community health professional – inclusive program	New technology utilization program	Community health professional – inclusive program, and New technology utilization program
All years: Implement the Clinical Investigation Team Building Program				

### **Summary: Transforming the Translational and Clinical Research Enterprises**

The portfolio of pilot programs already in existence at the University of Pittsburgh provides a solid foundation on which to model the proposed CTSI pilot programs which have been designed to overcome some of the barriers that continue to impede translational and clinical research. Already existing programs will be improved through heightened visibility and the addition of web-based tools that will facilitate communication among basic and clinical investigators. In addition, new pilot programs that model already existing, highly successful programs will be developed. Specifically, a CTSI-Collaborative awards program will be implemented. This program will fund collective research efforts that involve both clinicians and basic scientists. Further, a CTSI-Targeted Pilot program that allows clinical investigators to explore new technologies will be initiated. Additional pilot opportunities aimed toward allowing clinical researchers to define variables for appropriate study design or to engage community practitioners in clinical research will also be developed. These programs will support the transformation of the Translational and Clinical Research Enterprises at the University of Pittsburgh by facilitating the integration of basic scientists into the clinical research world and of clinical scientists into both the technology-laden culture of basic science and the community-based practices of health professionals.

**Literature Cited:**

1. Cincinnati Children's Hospital and Medical Center. The GCRC Protocol submission, Small and/or Pilot Studies page. Protocols which Propose "Pilot Studies" by Paul W. Stewart. Available at: [http://www.cincinnatichildrens.org/research/cores/gcrc/protocols/Small\\_or\\_Pilot\\_Studies.htm](http://www.cincinnatichildrens.org/research/cores/gcrc/protocols/Small_or_Pilot_Studies.htm). Accessed February 2, 2006.
2. Polit, DF, and Beck CT. *Nursing Research: Principles and Methods*. 7<sup>th</sup> ed. Philadelphia, PA; Lippincott Williams & Wilkins; 2004.
3. Organization for Autism Research. Frequently Asked Questions page. Available at: <http://www.researchautism.org/faq.asp>. Accessed February 2, 2006.
4. Librarian. Homepage. Available at: <http://bioinformatics.org/librarian/> Accessed February 10, 2006.
5. Perseus Development Corporation. Blog Studies, Blog Survey Weblog page. Available at [www.perseus.com/blogsurvey/blog/051223agerange.html](http://www.perseus.com/blogsurvey/blog/051223agerange.html). Accessed February 10, 2006.
6. Fox, S. *Older Americans and the Internet*. Washington, DC; Pew Internet & American Life Project; 2004. Available at: <http://www.pewinternet.org/topics.asp?c=2>. Accessed February 10, 2006.
7. Butler, D. (2005) Science in the web age: Joint efforts. *Nature* **438**, 548-549.
8. Wikimedia Foundation, Inc. Article: Science Blog page. Available at: [http://en.wikipedia.org/wiki/Science\\_blog](http://en.wikipedia.org/wiki/Science_blog). Accessed February 10, 2006
9. Scarpa, T. (2006) RESEARCH FUNDING: Peer Review at NIH. *Science* **311**, 41.
10. Ambion, Inc. Web Resource Pages: miRNAs: Definition & Overview, Available at: [http://www.ambion.com/techlib/resources/miRNA/mirna\\_intro.html](http://www.ambion.com/techlib/resources/miRNA/mirna_intro.html). Accessed February 6, 2006.
11. Alvarez-Garcia, Ines and Miska, Eric A. (2005) MicroRNA functions in animal development and human disease. *Development* 132, 4653-4662.
12. Carnegie Mellon University and Intel Research Laboratory at Pittsburgh. The Diamond webpage. Available at: <http://diamond.cs.cmu.edu/>. Accessed February 10, 2006.

***Transformation of the Scientist***  
**CTSI Regulatory Knowledge and Support**

The specific aims of the Regulatory Knowledge and Support Core of the CTSI are to:

1. Establish a CTSI Regulatory Knowledge and Support Core (RKSC) for three distinct groups of stakeholders
  - Research Community (clinical and translational investigators, research coordinators, dedicated research staff, basic scientists embarking on clinical research activities)
  - Lay Community (actual and potential research participants drawn from the in- and out-patient settings of the University of Pittsburgh Medical Center, and from the general population of Pittsburgh and the surrounding tri-state area)
  - Health Professional Community (individuals working within clinical and hospital settings – including physicians, nurses, therapists, technicians, dentists, pharmacists, and other health professionals – whose primary responsibility is to provide clinical care to patients)
2. Establish a Regulatory Compliance Facilitator Program to facilitate this Core and provide resources, services, training, and education that meet the unique needs of each group of stakeholders
3. Transform the GCRC Research Subject Advocates into Research Participant Advocates whose primary responsibility is to protect human subjects participating in research studies performed by all CTSI investigators at the University of Pittsburgh.

**BACKGROUND**

To be compliant with what seems to be an ever-increasing number of regulations, investigators conducting clinical trials must now submit their research protocols to myriad oversight committees that, in addition to the Institutional Review Board (IRB), may include a Conflict of Interest Committee, a Radiation Safety Committee, an Institutional Biosafety Committee, and a Fiscal Review Committee. In addition, protocols undergo prior scientific review to ensure that the study is well-designed and scientifically meritorious. Further, protocols must include an adequate data and safety monitoring plan as well as a recruitment plan that is fully consistent with the patient privacy protections mandated by HIPAA. Note that these regulatory requirements have been mandated by research sponsors (e.g., NIH), federal oversight offices (e.g., the DHHS Office of Human Research Protections; the FDA Good Clinical Practice Program), and academic medical centers – often in response to injuries or deaths to research subjects, or to complaints from subjects or the public.<sup>1</sup> Although these have been characterized by some commentators as “regulatory burdens”<sup>2,3</sup>, absent an academic medical center’s ability to rewrite the regulations, they become obstacles or impediments to clinical research *only* when their implementation at the institutional level is unnecessarily onerous or inefficient, and/or when it introduces significant delays in the initiation of clinical research studies.

Investigators have responsibilities associated with their multiple roles in an academic medical center that include research, clinical services, education, and administration. For clinical investigators, staying abreast of and having a full understanding of research regulations can be a difficult and time consuming task and may lead to unintentional non-compliance in the conduct of their research and lack of interest or enthusiasm to initiate or continue research activities. On the other hand, basic science investigators may be unfamiliar with the breadth and complexity of research regulatory requirements, or may perceive them as so burdensome that they are discouraged from entering the clinical/translational research arena. Although the University of Pittsburgh has, over the past 10 years, created a number of regulatory resources designed to overcome these barriers, utilization by investigators has been far less frequent than would be expected.

In addition to investigators, two other groups a critical role in the successful conduct of clinical trials yet often have little understanding of either the relevant ethical and regulatory protections or of standard clinical research procedures. Research subjects (or potential research subjects) comprise the first group. Individuals who are recruited into clinical research studies – either from a medical setting or from the community at large – must have a better understanding of the value of clinical research, the risks (and potential benefits) of such studies to themselves and to the larger community, the types of safeguards provided by research oversight



committees, the voluntary nature of their participation, and their rights as participants in research. A second group that contributes to the success of clinical research yet is often overlooked by investigators is the community of health professionals who provide clinical services to the patients participating in research studies. These individuals, who may be providing care to research subjects, must also follow specific research protocols that require them to record data and collect specimens in a very specific way (which may deviate from standard clinical practices), and have at least a basic understanding and appreciation of human subjects research so that they can address possible concerns or questions that may be asked of them by the patients participating in research studies.

## **Current State of Regulatory Programs at the University of Pittsburgh**

The University of Pittsburgh has developed a series of training programs, services, and resources to support investigators in conducting research responsibly and in protecting human subjects. Examples of current available offices, programs, resources and services include:

### Research Practice Fundamentals

Academic research institutions have long recognized the need to ensure that faculty, staff, and students are knowledgeable of the principles and requirements that are essential for the responsible conduct of research (RCR).<sup>4,5</sup> Throughout the past decade, well-publicized cases of research misconduct have emphasized the need for the scientific community to address the quality and variability of RCR training.<sup>6</sup> As a result, in 2000, the University of Pittsburgh's Senior Vice Chancellor for the Health Sciences issued a directive for the development of a proactive, comprehensive, and scalable approach to RCR training. A multidisciplinary group of approximately 25 stakeholders from the Schools of the Health Sciences and the general university administration directed the development and implementation of a training solution. In January 2001, the University of Pittsburgh launched an internet-based education and certification program (Research and Practice Fundamentals [RPF] <https://rpf.health.pitt.edu/rpf/>) to support the related training needs of its research community.

The RPF program consists of educational material organized into modules by topic. Each module is composed of two components, a knowledge acquisition section that delivers the content and a knowledge demonstration section that allows the user to apply the content and demonstrate mastery. Certification is obtained by successfully answering a series of questions about the topics covered by the module. Continuing Medical Education (CME) and Continuing Education Units (CEUs) are available upon completion of each module. Certification requirements vary per module; for example, all persons involved in health sciences research at the University of Pittsburgh and its affiliated institutions are required to complete training in Research Integrity. Individuals involved in research involving human subjects are required to complete training in Human Subjects Research, and individuals conducting experiments on animals must complete the Laboratory Animal Research module. The certification status for each participant is recorded in a database and is tracked for administrative and evaluation purposes. Key institutional offices (i.e., Institutional Review Board, Institutional Animal Care and Use Committee, and Office of Research) have administrative access to the database for purposes of confirming compliance with certification requirements. The processes for verifying completion of training requirements will be further facilitated by the development of interfaces between the RPF certification database and the process management systems that each of these offices is currently implementing.

RPF currently consists of 17 modules: 1) Research Integrity; 2a) Human Subject Research for Biomedical Researchers; 2b) Human Subject Research for Psychosocial Researchers; 3) Laboratory Animal Research; 4) Conflict of Interest; 5) Human Embryonic and Stem Cell Research; 6) HIPAA Privacy for Researchers; 7) HIPAA Privacy for Staff; 8) HIPAA Privacy for Health Care Providers; 9) Blood-Borne Pathogens; 10) Chemical Hygiene; 11) Responsible Literature Searching; 12) IRB Member Education; 13) Research Involving Children; 14) HIPAA Security for UPMC Staff; 15) HIPAA Security for UPMC Physicians; 16) HIPAA Security for University of Pittsburgh Providers and Staff; and 17) Good Clinical Practice. As of February 1, 2006, the RPF program had 25,025 registered users and had issued 62,165 certifications.

### The Education and Compliance Office for Human Subject Research

The mission of the Education and Compliance Office for Human Subject Research (ECO-HS) is to promote research excellence and integrity throughout the University by performing audits of the conduct of human

subject research studies and by providing education related to good clinical research practices to University faculty, staff and students. Since its inception in November, 1996, this office has expanded from a staff of one to a staff of four full-time coordinators – all of whom have had a background in nursing and in research. In order to fulfill its mission, the ECO-HS performs investigator site audits, conducts quality assurance (QA) interviews prior to the implementation of a research project, organizes educational seminars for the Pitt Research Network, monitors the informed consent process, assists with the University's Orientation Program for Clinical Research Coordinators, and provides support to a variety of human subjects programs on an as-needed basis.

Conducting investigator research project audits is a particular strength of the ECO-HS. These audits involve an extremely detailed and lengthy process that encompasses review of the entire associated IRB file with the development of an IRB submission timeline, development of study specific audit tables, pre and post audit interviews, review of research records for approximately 20% of total study enrollment subjects, the issuance of a detailed audit report, IRB Executive Committee review of the audit report, and review of investigator responses to the audit, and post audit correspondence resulting from the IRB Executive Committee review of the associated report and correspondence. Audits may be conducted on randomly selected protocols supported by federal or internal funds although protocols are often selected for audit based on criteria such as degree of risk, participation of multiple study centers, involvement of an investigator sponsored Investigational New Drug (IND), gene transfer intervention, and/or inclusion of radioactive drug research.

Since the implementation of this auditing program, there has been a marked improvement in the documentation of informed consent and overall study documentation. Nevertheless, concerns remain that the audit program is not sufficiently far-reaching. In response, the ECO-HS modified its methods for conducting audits in 2005, and is now implementing department-based audit plans as opposed to randomly selected individual investigator site audits. It has also increased the number of pre-study implementation QA interviews. These QA interviews/audits are conducted on newly approved studies prior to any enrollment of research participants. The interview focuses on the processes the investigator has in place to conduct the research study such as staff training systems, documentation methods, data safety monitoring, etc. Because the QA Interview is conducted on newly approved studies prior to enrollment of any research subjects, it can be conducted in less than half the time required of full investigator site audits. Due to the fact that this interview is held prior to subject enrollment, it offers the potential to prevent protocol deviations and improve research study documentation.

#### Conflict of Interest Office

The Conflict of Interest (COI) Office was established in February 2004 to support the functions and activities of the University's COI Committee (COIC) and Entrepreneurial Oversight Committee (EOC). The COIC is responsible for the oversight and management of potential conflicts of interest (COIs) of the University's employees and the institution, including those involving human subject research. The COIC developed a standard management plan that is invoked by the University's Institutional Review Board (IRB) when an investigator has a potential conflict with a research study. The EOC, a standing subcommittee of the COIC, reviews conflicts related to technology transfer and activities involving start-up companies.

To promote awareness and understanding of COI issues, the COI Office and the chair of the COIC provide ongoing educational opportunities, training, and resources to the University community; among these are: 1) an extensive COI Web site (<http://www.rcco.pitt.edu/coi/>), which includes convenient links to federal COI regulations and University COI policies; 2) customized COI presentations to deans, department chairs, academic units, groups of investigators, and other members of the University community, provided when requested (or upon proactive solicitation on the part of the COI Office); 3) maintenance of a close working relationship with and education of IRB personnel concerning COI issues and procedures; 4) an online COI "Research and Practice Fundamentals" training module that must be completed by researchers with outside financial interests and those conducting industry-sponsored research (<http://www.rcco.pitt.edu/coi/education/COIeducation.htm>); 5) a library of case studies to assist supervisors in managing their employees' potential COIs, available online through the COI Web site: <http://www.rcco.pitt.edu/coi/CaseStudies/COICaseStudiesMenu.htm>; and 6) *A Guide for Investigators*: (<http://www.oorhs.pitt.edu/Documents/Guide.cfm>) which contains a listing of offices and departments within the University that play a central role in the University's research mission.

The COI Office staff is composed of a director, a compliance coordinator, and an office coordinator. Knowledgeable in COI matters, the 28-member COIC and EOC represent a broad spectrum of University administrators, faculty, staff, and students involved in research and purchasing. The Office and the committees report to the Vice Chancellor for Research Conduct and Compliance.

#### OSIRIS: Online Submission for Institutional Review

OSIRIS is a comprehensive, internet-based system for the submission and tracking of IRB protocols and all related documents (e.g., consent forms; investigator brochures). Using a fully interactive format, OSIRIS provides an opportunity for an investigator to be queried about the regulatory requirements during the preparation of the application. This query is accomplished with a series of questions that are integrated into what are termed "smart forms." Each smart form page contains written text or links to educational materials appropriate for the questions being asked. The investigator and research staff are able to request assistance at anytime using a HELP link located on each page. This question/answer format prompts investigators (and the IRB reviewer) to: 1) consider all applicable ethical and regulatory issues; 2) ensure that all relevant procedures (e.g., details of recruitment process) and study risks are fully described; 3) facilitate a comprehensive discussion of ethical and regulatory issues during preparation and review; and 4) improve consistency in the review process. The system is flexible insofar as it enables the IRB to easily add questions to address new issues and regulations as they arise.

To permit direct communication between the investigator and research staff, review entities, and the IRB, OSIRIS utilizes automated e-mail notification. Since the system is an internet-based product, the investigators can oversee all aspects of their IRB submission anywhere in the world, and IRB reviewers can similarly access protocols (and supporting documentation) from any computer with an internet connection. The system also tracks reports of adverse events and other unexpected problems, modifications, and renewals, as well as ancillary reviews (e.g., external scientific review; hospital fiscal review). IRB Committee meetings are paperless, and because all documentation is electronic, administrators from a variety of entities (e.g., CTSI) can readily obtain access to some, or all, information about an investigator's IRB submission (depending on permissions provided to the administrator by the IRB). The automated logging and tracking system permits quantification of IRB processing efficiency, and the database organization of the system permits ready identification of certain types of protocols, from certain types of investigators, for various quality assurance and outcome studies. This system is now being introduced to the University community, and it is expected that all new IRB submissions will be on-line before the end of 2006.

OSIRIS is only one component of the University of Pittsburgh IRB, which was recently accredited by the Association for the Accreditation of Human Research Protections Programs. The University of Pittsburgh IRB serves as the IRB of record for University of Pittsburgh faculty, students or staff who are engaged in the conduct of human subject research and also serves in that capacity for several affiliated institutions, including UPMC (which includes University of Pittsburgh physicians [UPP]), Children's Hospital of Pittsburgh, and Magee Women's Research Institute. In the fiscal year 2005, the **total number of active protocols was 5,698**. In the Health Sciences Area (including Schools of Medicine, Public Health, Health and Rehabilitation Sciences, Nursing, Dental Medicine, and Pharmacy) there were 1,483 full board protocols, 1,426 expedited review protocols, and 1,473 exempt protocols. To complete full board review of submitted protocols in an efficient manner, new protocols are assigned to one of 10 review committees, three of which are dedicated to 'special populations' (two committees focus on pediatric research, one focuses on pregnant women, neonates, and fetuses). Currently, six Vice-Chairs are responsible for conducting meetings. Board membership currently includes a total of 184 scientific members, 42 non-scientific members, 38 community (i.e., non-affiliated) members, three prisoner representatives, and 34 alternate members. Note that some members fall into two categories; total active membership is 239. Expedited and exempt reviews are handled administratively by staff members under the direction of an additional Vice-Chair. Twenty-four IRB staff members are available to process protocols, and work with investigators to help develop protocols and consent forms and to address questions. Educational sessions include twice-a-month "Ask the IRB" sessions, and frequent programs provided to students, fellows, research coordinators, and investigators.

#### Institutional Data and Safety Monitoring Board (IDSMB).

To assist investigators with the process of complying with the NIH mandated data and safety monitoring requirements for all Phase I, II and III clinical trials, the Office of Clinical Research, Health Sciences, (OCR) created an Institutional Data and Safety Monitoring Board (IDSMB) in 2002. OCR organizes and administers

data and safety monitoring through a pool of clinical investigators who have experience and/or expertise in various areas of clinical research. These clinical investigators are faculty from the six schools of the health sciences. The IDSMB personnel also assist with preparing data and safety monitoring plans and assessing the need for a data and safety monitoring board.

Responsibilities of the IDSMB include: 1) evaluation of clinical trial progress, including safety assessments, 2) assessment of whether the ongoing trial can be realistically expected to achieve its primary objective, taking into account the accrual rate and occurrence of an unexpectedly high rate of severe or life-threatening adverse events that may dictate recommendation for premature closure of the trial, 3) consideration of factors external to the study, when relevant, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial, 4) protection of the safety of the study participants, and 5) if appropriate, conduct of interim analysis of efficacy and toxicity in accordance with stopping rules that are clearly defined in the protocol.

To date, the IDSMB has received more than 25 requests, which are in various stages of the research process and are projects that have received funding from the NIH, industry sponsors, or individual departments.

#### Protecting Research Subjects: A Skills Workshop for Investigators and Coordinators

The protection of participants is paramount during the conduct of human subject research. Government agencies and professional organizations agree that investigator education in the ethics of research is an essential component of a human subject protection plan.<sup>7-9</sup> Training in research ethics is mandatory for National Institutes of Health (NIH) research award recipients.<sup>10</sup> Knowledge of abstract ethical principles, however, is an insufficient safeguard for the ethical conduct of research. There is a growing awareness that the practical application of ethical principles, especially in the area of investigator-subject communication and informed consent, remains inadequate, with the result that study subjects often consent to participate in clinical research without understanding either the true aims of the research or the actual risks and benefits.<sup>11,12</sup>

Despite the breadth of activities promoting the responsible conduct of research, it was recognized in the early 2000s that the objective of the existing programs was related to the acquisition of knowledge about regulatory requirements and institutional policies and procedures. While this approach is obviously important, it was clear that the improvement of certain competencies, such as obtaining adequate informed consent, would be achieved best by addressing both gaps in knowledge as well as deficiencies in skills and attitudes. In 2003, the University of Pittsburgh received a grant through the NIH National Center for Research Resources (SO7RR18239) to develop a pilot educational activity to improve competency in obtaining formed consent.

A multidisciplinary group met monthly for a period of nine months to plan the activity. It was determined that the intervention should 1) provide background information on the regulatory and ethical context for informed consent, 2) be relevant to the participants' own research protocols, and 3) offer an experiential component in which individuals could practice their skills at obtaining consent and receive constructive feedback.

A set of 32 skills based on ethical concepts, communication strategies, and adult learning principles were defined and incorporated into a one-day workshop. Instructional methods included an interactive lecture, a video illustrating communication skills, and a session where participants used their own currently active research protocols to obtain informed consent from standardized patients (SPs) who portrayed four subject "types": distrustful, adolescent attitude, mild dementia, and overly eager. SPs rated participants' skills using a checklist and provided feedback immediately followed the session. Knowledge was assessed with pre/post video questionnaires. Program effectiveness was evaluated by participants at the session and at three months using a scale from one (lowest) to five (highest).

Fifteen experienced investigators and coordinators participated in the workshop, four of whom were physicians. The remaining attendees listed their role as "research coordinator." There was a statistically significant number of skills identified on the post-test video questionnaire (mean 7.1 versus 8.7,  $p < 0.05$ ). All but four (75%) of the participants scored above 80% on the SP evaluation checklist. The SPs were identified as the most useful part of the program by 71% of participants at the session and 86% at three month follow-up. Participants reported that the material presented was new (mean 3.5) and interesting (mean 4.2); that the course met their expectations (mean 4.4), and that the course made a positive difference when communicating with potential subjects (4.5). All of the participants reported that they would recommend the program to a

colleague. This innovative curriculum was well received and effective for teaching communication skills that facilitate the informed consent process.

### Research Subject Advocate (RSA)

The primary focus of the Research Subject Advocates of the General Clinical Research Centers (GCRCs) is to ensure that studies conducted on the GCRCs are designed and conducted safely and ethically with protection of human subjects as the highest priority (NCRR guidelines). The RSAs assist investigators with the development or modification of Data and Safety Monitoring Plans (DSMPs), with their execution, and with any DSMP-related issues, such as subject safety, privacy, data quality, confidentiality, timeliness, and efficacy. The RSAs also participate in the review of protocols submitted to the GCRC Advisory Committee (GAC). The RSAs at the University of Pittsburgh have created a protocol tracking application that includes New Protocol Data, Adverse Events, Protocol Renewal, Modifications, Protocol Deviations/Violations, Administrative/Clinical Holds, and Information Request Log (to track outstanding documents). Specific features of this application include: accrual rate calculation, assessment of DSMB requirement and a search function for specific study drugs, devices and biologics. The RSAs monitor the adverse event database on a routine basis to identify potential trends within a given protocol that may warrant further review and subsequent discussion by the GAC. The RSAs also act as the liaison between the investigators, the GAC and the IRB, and provide education to investigators, coordinators and GCRC staff when such a need is identified. Currently, at the University of Pittsburgh Academic Health Center there are 1.5 FTE RSAs: 1 FTE addresses concerns at the University of Pittsburgh adult GCRC; 0.5 FTE addresses concerns on the much smaller Children's Hospital of Pittsburgh pediatric GCRC.

RSAs are also available to provide oversight regarding assent and consent procedures and in the implementation of study protocols. If requested by study or GCRC staff, the RSAs may observe the informed consent process, and when required, can address subjects' concerns, or any other issues related to research taking place in the GCRC.

### **Summary of Existing Resources**

Existing programs and resources are available at the University of Pittsburgh to promote and support regulatory knowledge in the conduct of clinical and translational research. However, because these resources are maintained by various offices and programs across the University, it may be particularly difficult for new investigators to access them efficiently. That is evidenced by discrepancy between the number of potential investigators who could benefit from these services and the number of investigators who actually use these services and attend the programs. Unsolicited feedback from investigators and research coordinators has also indicated that had they been aware of the resources available to assist them in preparing research protocols, their submission would have been more efficient and effective, with far less stress and anxiety.

### **CTSI REGULATORY KNOWLEDGE AND SUPPORT CORE: DESIGN AND METHODS**

**Overview: What transformations will be made?** Regulatory compliance is critical to sustaining and transforming the clinical and translational research enterprise at the University of Pittsburgh. As described above, several programs have been created to assist with regulatory compliance, but their existence is often unknown to researchers. These programs are managed by different entities, and were often developed initially to serve the needs of a very specific group of stakeholders. The CTSI will transform regulatory compliance education and training, services and resources from a decentralized system into to a highly integrated Regulatory Knowledge and Support Core (RKSC) that can serve as a readily accessible resource for all individuals participating in clinical and translational research activities at the University of Pittsburgh. To that end, currently available resources will be enhanced, and new programs will be specifically designed to meet the needs of researchers, research participants, and health professional partners. This goal will be accomplished by 1) reviewing existing research regulatory resources and assessing their appropriateness for enhancement, 2) identifying gaps in the current regulatory compliance education and training programs and services, 3) creating new education and training programs, resources, services and tools that bridge those identified gaps, and 4) evaluating the effectiveness of all education and training, resources, services and tools in improving regulatory compliance and research subject satisfaction.

Further, the current General Clinical Research Center's Research Subject Advocates (RSAs) program will be transformed and extended into a Research Participant Advocates (RPAs) program for the entire CTSI. The

Research Subject Advocate (RSA) system developed within the GCRC structure will be used as a basis for the new RPA program, but will be modified for optimal use. The primary responsibility of the RPAs will be to protect human subjects by ensuring that 1) there has been an accurate and safe translation of a research proposal into a research patient protocol (e.g., to include doctors' and nurses' orders, research patient management procedures, appropriate documentation, etc.), 2) data and safety monitoring plans are appropriately implemented, and 3) research subjects' questions, concerns and complaints are addressed rapidly and to the satisfaction of the subjects and/or their families. These services will be made available to all CTSI investigators and all actual and potential participants in studies that are conducted by CTSI investigators at the University of Pittsburgh

### Organizational Structure:

The RKSC will include the Director (Laurel Yasko), an Administrative Assistant, the Regulatory Compliance Facilitator, Research Participant Advocates (Jane Alexander, Michael Green, M.D. and Eva Vogeley, M.D., J.D.), and the Health Professional Educator (TBN), all of whom will work closely to accomplish the specific aims of this Core (Figure 1)

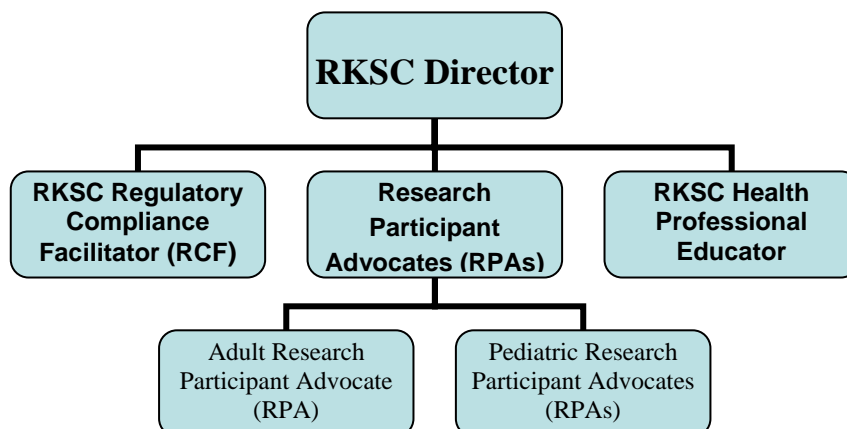


Figure 1. RKSC Administrative Structure

This Core serves three groups of stakeholders (Figure 2):

1. the research community – defined as clinical research investigators, research coordinators, and research staff as well as basic science investigators and research staff;
2. the lay community – defined as actual and potential research participants at the University of Pittsburgh and the University of Pittsburgh Medical Center (UPMC);
3. the health professional community – defined as nurses, technicians, and other health professional staff at UPMC.

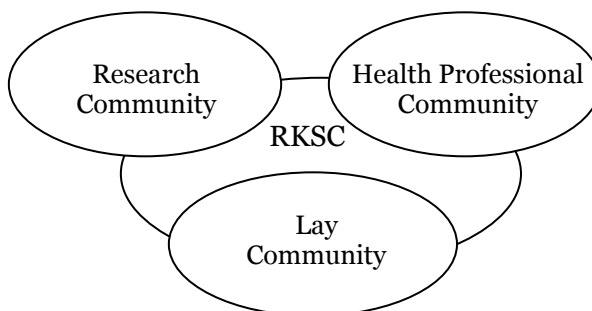


Figure 2: Stakeholders who will be served by the RKSC

### Research Community:

The RKSC will provide “researcher-focused” support for regulatory compliance and management. The primary intervention for the research community will be to provide services, education and training, tools and resources to assist investigators with the responsible conduct of research from a single, integrated source.

### Services

Key to the success of the CTSI Regulatory Knowledge and Support Core is the Regulatory Compliance Facilitator (RCF). This individual will integrate and organize all existing resources and services on research regulations and will help develop new materials and training programs, so that researchers can easily obtain access by contacting a single office. Drawing on his or her expertise in research regulations, the RCF who is independent of the IRB, will interact closely with members of the University Research Conduct and Compliance Office (which includes Institutional Review Board, Institutional Animal Care and Use Committee, Institutional Biosafety (rDNA) Office, Education and Compliance Oversight for Human and Animal Research, Embryonic Stem Cell Research Oversight Committee, and Radiation Safety Committee) to stay current with federal and institutional regulations, policies and procedures and to ensure that CTSI researchers have the requisite knowledge to be in complete compliance with all requirements governing human subjects research. A senior member of the University of Pittsburgh IRB leadership will interact with the regulatory support personnel at other CTSA institutions through the National CTSA Regulatory Support Steering Committee to ensure that collaborative clinical and translational research activities are facilitated.

The RCF will proactively schedule individual meetings with all new faculty of the University of Pittsburgh as well as junior investigators, students, and others (as requested or identified) to orient them to services and resources available in the CTSI RKSC. The RCF will also be available to all CTSI members to assist with identifying new or updated education and training programs and with communicating and providing access to services and resources available to enhance compliance for individual research projects.

The RCF and the RPA will work together to provide support to CTSI investigators using the CTSCs (See CTSI Participant and Clinical Interactions Resources), junior investigators, students, and others (as requested or identified) by assisting with protocol and consent form development, ensuring accuracy of consent forms, ensuring appropriateness of Data Safety Monitoring Plans, assisting with monitoring and reporting plans of adverse events, and reviewing proposals to ensure that study procedures are accurately translated into appropriate research patient protocols.

Due to the additional protections afforded by the federal regulations (45 CFR 46, Subpart D) for children participating in research, the RPAs for the pediatric population will continue to provide human subject protection review and monitoring for all protocols that are conducted on the Children's Hospital Clinical and Translational Research Center (CTRC) - formerly the Children's Hospital GCRC. In addition to initial and annual review, the pediatric RPAs will assist investigators with the development and execution of appropriate Data and Safety Monitoring Plans (DSMPs), and with any DSMP-related issues, such as subject safety, privacy, data quality, confidentiality, timeliness, and efficacy. Adverse events will continue to be reported to RPAs, who will review and track them on a routine basis to identify emerging unexpected risks within a given protocol that may warrant further review.

The RPA program will eventually be expanded to support all CTSI investigators at the University of Pittsburgh. Once the effectiveness of this program has been evaluated and established, additional funds for complete expansion will be sought.

The RKSC will identify and evaluate existing services related to regulatory compliance and assess the applicability for collaboration, extension, and centralization to the entire CTSI community and implement as appropriate. Within this process, regulatory-compliance related service gaps will be identified and new services will be created based on these gaps. The CTSI Regulatory Compliance Facilitator (RCF) will be the central point person who will be dedicated to promoting and assisting investigators in gaining access to these services.

One important service that will be created as part of the CTSI is an Investigational New Drug (IND) and Investigational Device Exemptions (IDE) Applications Service. This program will be created to educate and assist researchers who are new to this area of research and to provide a centralized resource for researchers who may not have the knowledge or resources available to apply for INDs or IDEs. The objectives of the service will be to 1) ensure that all University of Pittsburgh researchers who need to file an IND or IDE do so correctly, and 2) clarify the complex regulations and responsibilities set by the U.S. Food and Drug Administration (FDA) for IND/IDE. This service will assist researchers in the preparation of IND/IDE and create a checks and balances system for each project to track submission progress and continuation reports to

the FDA and other required agencies to ensure consistency and compliance with the regulations related to IND/IDE.

An existing service that will be expanded as part of the CTSI is the Institutional Data and Safety Monitoring Board (IDSMB). This will be promoted to all CTSI members who require a data and safety monitoring board for their study and require assistance in setting up the board and coordinating the continual reviews of the board. This service will also include assistance with data and safety monitoring plans and determining whether a data and safety monitoring board is necessary. Coordination of an IDSMB committee will consist of 1) obtaining appropriate board members with assistance of the principal investigator as appropriate, 2) coordinating meetings and preparing meeting minutes and data and safety monitoring reports that will be submitted to the required agencies, and 3) providing assistance to investigators for changes to their study as requested by the DSMB review.

Ongoing evaluations of these services will be conducted, and changes to the current services and creation of new services will be implemented as appropriate.

#### Education and training:

Education and training are critical for enhancing the responsible conduct of research. The CTSI RKSC will identify and evaluate existing formal and informal education and training programs related to regulatory compliance and the responsible conduct of research and assess the applicability for expansion to the entire CTSI community and implement as appropriate. Within this process, identified education and training gaps will be addressed by developing new didactic and interactive seminars and training programs.

Examples of new training seminars that will be created to enhance Clinical and Translational research activities include the following:

- “What’s New in Research Regulations?” Because research regulations and requirements are periodically revised, and new guidances promulgated, a series of update sessions for investigators and coordinators will be conducted. For example, a program that summarizes the recently released FDA rule and new guidance on the investigational new drug (IND) application process will be developed.
- “Good Research Practices Seminars” To facilitate translational research as it relates specifically to drug development, a series of seminars that address Good Laboratory Practice, Good Manufacturing Practice, and the Investigational New Drug Application process will be developed. Individuals at the University of Pittsburgh have experience in working with the FDA on studies involving Investigational New Drug Application procedures. These individuals will present at periodic seminars that will focus on the regulations, process design, process controls, resource allocations, management responsibilities, the crucial differences between “quality” and “compliance,” return-on-investment issues (lower costs, improved controls, and faster FDA review and approval of new products), and best practices for success involved with these important translational activities. Also included in this seminar will be Phase I manufacturing training and updates on new regulatory requirements and resources available to assist with these regulations and submissions.
- “Good Clinical Research Practices Seminars” To educate investigators and research staff involved in FDA and non-FDA regulated human subject research projects, a Good Clinical Practice seminar will be conducted periodically. The information presented in this program will be based on the “Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance” and will rely on techniques pioneered in our “Protecting Research Subjects: A Skills Workshop for Investigators and Coordinators” (see Part B). This program will focus on Good Clinical Practice (GCP), ethical considerations, human subject protection, the informed consent process, responsibilities of the principal investigator, and resources available to assist researchers and staff in complying with GCPs. This training will also be available to groups or individuals upon request.

The RKSC will provide instructional material to clinical research investigators, basic science investigators, coordinators and health professionals. In regard to accessibility, the attribute that all of these groups have in common is diversity of time and location. This diversity means that the RKSC will need to provide distance education for both synchronous and asynchronous instructional events. The RKSC will utilize the CSTI Center for Clinical and Translational Informatics (CCTI) Learning Center (see Center for Clinical and Translational



Informatics) to provide education and training seminars via Webcasts (both real-time and archival) for individuals who cannot be present at the time of the seminar.

For all education and training coordinated through the CTSI RKSC, Continuing Medical Education (CME) and Continuing Education Unit (CEU) credits will be given.

#### Resources and Tools:

The RKSC will identify and evaluate all existing regulatory compliance related resources and tools and assess their applicability for extension and centralization to the entire CTSI community and implement as appropriate. Within this process, regulatory compliance related resources and tool gaps will be identified and new resources and tools will be created based on these gaps. The RKSC will interact with the Education and Compliance for Human Subject Research, the Education and Compliance for Animal Research, and the CTSI Online Research Community development group (see CTSI Center for Clinical and Translational Informatics) to create a frequently updated repository of resources and tools that will be web-based and easily modifiable for specific research projects. Examples of tools that will be included are:

- Informed consent form templates and standard language, at the appropriate reading level, for common research procedures and assessments
- Case report form templates for study documentation that can be customized for individual studies
- Specific forms (i.e., screening and eligibility logs, adverse event forms, evaluation forms)
- Regulatory report template forms and tracking databases.

This interactive “intelligent” web-based system will provide resources and tools based on the individual study. The availability of this website will be communicated throughout the University of Pittsburgh using a multi-media approach including presentations by the program manager, links to the site from other websites, email notifications, and printed materials.

Adverse events (internal and external) will be reported and tracked utilizing the OSIRIS IRB web-based submission system. The RCF will provide instruction to investigators requesting assistance with reporting adverse events to the FDA and other required agencies and sponsors.

The OSIRIS IRB web-based submission system will also be used to provide links to appropriate resources or tools to assist investigators in preparing and conducting their research projects.

#### **Lay Community:**

There are two innovative features of the RKSC planned establishment of a human subject protection program for potential research subjects (i.e., members of the “lay” community). First, educational materials and programs for both patients and nonpatients will be developed to inform them about the potential value of clinical research to them, their families, and to the larger community. Second, individuals who can serve as advocates for research study participants and who can address questions, concerns, and complaints about the details of a study or their rights as human subjects will be employed. Although the IRB currently has a human subjects protection advocate, that individual typically addresses subjects’ complaints (most often, dealing with payment issues, or billing) that emerge after an individual has completed a study. The current General Clinical Research Center’s Research Subject Advocates (RSA) program will be transformed and expanded into a Research Participant Advocates (RPAs) program of the CTSI. The primary responsibilities of these RPAs will be to protect human subjects and, therefore, to provide their services to all actual and potential participants in studies that are conducted by CTSI investigators at the University of Pittsburgh. The RKSC will include an RPA with broad expertise in clinical research activities for the adult population and RPAs with pediatric expertise for the child/family population. The RPAs’ roles and responsibilities will include educating and advocating for actual and potential research participants, and providing proactive support to participants – or potential participants – as they enter a study or during their participation in the study.

The RPA will be the primary contact person for all actual and potential research participants and their families to answer general research related questions and address concerns or complaints related to a specific research project. The contact information for the RPA will be included in the informed consent documents, communicated to research and health professional staff, and communicated via research related websites,

brochures, posters, etc. A database (RPA Participant Contact Database) will be created to track the RPA's contacts with participants; questions asked; misunderstandings; and complaints.

The RPA will assess study participants' understanding of the informed consent process and the research study in which they are enrolled. The RPA will collaborate with the Education and Compliance Office to evaluate the informed consent audit data and will compare this to their ongoing assessment of study participants' knowledge of the informed consent process and the research study in which they are enrolled. The data will be evaluated to determine common questions and misunderstandings associated with the informed consent document, with the research process, and with the research evaluations and procedures conducted. This data will be correlated with the RPA Participant Contact Database to ensure that all areas are being addressed. Based on the results of the data analysis, the RPA will implement plans for addressing these areas of misunderstanding and concerns.

The RPAs will act as the liaison between the investigators and participants and the Institutional Review Board and other institutional offices and committees with human subject protection responsibilities. Common questions and misunderstandings of participants will be brought to the attention of these offices and committees.

The RPA will collaborate with other cores of the CTSI to assist in the development of participant-focused educational materials and presentations to current and potential research participants either individually or in groups.

### **Health Professional Community:**

The primary intervention for the health professional community will be to provide education, training, and resources that describe the importance and value of the responsible conduct of research.

### Education and Training

The RKSC will assess the regulatory education and training needs of the health professionals at the University of Pittsburgh Medical Center (UPMC) Presbyterian and Shadyside hospitals. These hospitals are the primary locations where most of the research conducted by University of Pittsburgh faculty members is performed. Initially, health professionals at these locations, including nurses, technicians and others directly involved with patient care both inpatient and outpatient, will be surveyed on their understanding and perception of the conduct and value of clinical and translational research. Based on this survey, the RKSC Health Professional Educator will develop an educational in-service presentation. The presentation will be accessible to health professionals in various forums, including continuing education in-services and as a web-based training module. This presentation will include the ethical considerations of research, the importance of following a research protocol, and resources available to current and potential research participants. The presentation content will be evaluated by investigators, health professionals, and health professional educators prior to its implementation. This pilot project will be evaluated and modified as necessary and extended to other hospitals and outpatient offices throughout UPMC as it evolves.

### Resources

The RKSC will create research regulatory compliance related resources aimed to assist health professionals who care for current and potential research participants. These resources will be compiled, created, and made available on the CTSI website. Examples of resources that will be included are:

- Frequently Asked Questions (FAQs) related to the responsible conduct of research for a health professional involved in the care of current or potential research participants.
- Contact information for personnel involved in human subjects protection, including the Institutional Review Board (IRB), and the Research Participant Advocate (RPA)
- Updates on studies being conducted at the University of Pittsburgh and results of studies that have been completed.
- New information that will assist health professionals in the responsible conduct of research.

Notification of this website will be communicated during the in-service presentations and through email distribution lists and other sources of communication for the health professional community (e.g. links from the UPMC InfoNet portal).

## **Evaluation and Outcomes**

The Regulatory Knowledge and Support Core proposes several education and training programs, services and resources for the research community, lay community, and health professional community. The effectiveness of this proposal will be evaluated by assessing RKSC services utilization. This will be accomplished by tracking the number of people from the research community, health professional community, and lay community who approach the RKSC for services. A tracking system will be created for both the Regulatory Compliance Facilitators and Research Participant Advocates so that they can document every contact they have with one of the three stakeholders. Through the tracking system, a determination as to which services are utilized most widely, or not at all, will be made. Based on this information, services and programs will be modified accordingly. Those people who have utilized the core will be surveyed. These individuals will be asked which services they used and/or programs they attended and to what extent the services and programs were useful. The extent to which the services and programs satisfied the needs of core users will also be assessed. For additional details, see the CTSI Evaluation and Tracking Plan Section.

## **Proposed Timeline for Implementation**

During the first six months of the RKSC, efforts will be directed to start-up activities. The first activities will be to identify existing research regulatory resources and assess gaps and applicability for expansion of current activities for the research community; transform the RSA responsibilities into the RPA for the lay community; and conduct the regulatory education and training assessment survey for the health professional community. During the second six months, services, resources, and programs will be developed and necessary materials prepared. The first offering of each of the initiatives will take place in the second year, including the promotion of the Regulatory Compliance Facilitator, services, resources and education and training initiatives for the research community. In addition, the RPA informed consent and participant focused educational material initiatives will be established for the lay community and the educational in-service presentation and resources will be developed for the health professional community in the second year. Following the second year, the focus will include a thorough review of services, resources and programs along with evaluations, allowing for adjustments to be made with input from the CTSI Executive Committee and the Research Conduct and Compliance Office.

## **Summary of the Regulatory Knowledge and Support Core**

Many resource and educational opportunities are currently available to the research community but may not be readily accessible because of their dispersion across multiple programs and offices. In contrast, few resources and educational activities are currently being provided for either the lay community or for the health professional community. The CTSI recognizes the importance of developing an effective partnership between investigators, human subjects, and the health care professionals who may provide care to patients participating in research studies. The proposed CTSI Regulatory Knowledge and Support Core will facilitate that partnership in the following ways. The establishment of a centralized regulatory support core will provide investigators with ready access to a variety of resources that clearly and completely address local and federal regulations (including access to a regulatory “expert” – the Regulatory Compliance Facilitator – as well as appropriate forms and educational programs). This will help investigators more successfully and efficiently navigate the various rules associated with conducting studies involving human subjects, leading not only to better protection of human subjects but also to improved regulatory compliance. For potential research participants, the expansion of responsibilities of the Research Participant Advocates (formerly Research Subject Advocates) will empower patients, as well as non-patients drawn from the community, to articulate their concerns and questions prior to, or during, a particular research activity, thus allowing them to be fully informed about the risks, benefits, and procedures associated with a particular research study. The development of in-service programs and other educational programs designed explicitly for health professionals will ensure that all health care professionals at the medical center have a better awareness of research practices and procedures. This will enable investigator to not only follow specific research protocols in which their patients are participating, but also to address general questions or concerns about research raised by those patients. The use of the RKSC to provide support for research subjects and health care professionals, as well as for researchers, is a major transformational shift at the University of Pittsburgh. This is an important step in recognizing and supporting the unique contribution made by each of those three groups in the ethical conduct of clinical research studies.

**Literature Cited:**

1. Shalala D: Protecting research subjects -- what must be done. *N Engl J Med* 343:808-810, 2000
2. Sung NS, Crowley WF, Genel M, Salber P, Sandy L, Sherwood LM, Johnson SB, Catanese V, Tilson H, Getz K, Larson EL, Scheinberg D, Recce EA, Slavkin H, Dobs A, Grebb J, Martinez RA, Korn A, Rimoin D: Central challenges facing the national clinical research enterprise. *JAMA* 289:1278-1287, 2003
3. Pober JS, Neuhauser CS, Pober JM: Obstacles facing translational research in academic medical centers. *FASEB J* 15:2303-2313, 2001
4. National Bioethics Advisory Commission (NBAC). 2001. *Ethical and Policy Issues: Research Involving Human Participants*. 2 vols. Rockville, MD: US Government Printing Office.
5. Institute of Medicine National Research Council of the National Academies. *Integrity in Scientific Research. Creating an Environment that Promotes Responsible Conduct*. Washington DC: National Academy Press, 2002.
6. Blumenthal D. Academic-industrial relationships in the life sciences. *NEJM* 2003;349:2452-9.
7. National Bioethics Advisory Commission (NBAC). 2001. *Ethical and Policy Issues in Research Involving Human Participants*. 2 vols. Rockville, MD: US Government Printing Office.
8. American Association for the Advancement of Science (AAAS). 1993. Project 2061. *Benchmarks for Science Literacy*. New York: Oxford University Press.
9. Public Health Service. 2000. "Policy on Instruction in the Responsible Conduct of Research (RCR)."
10. NIH *Guide for Grants and Contracts*. "Required Education in the Protection of Human Research Participants." Notice OD-00-039. June 5, 2001.
11. Paasche-Orlow MK, Taylor HA and Brancati FL. Readability standards for informed consent forms as compared with actual readability. *New England Journal of Medicine*, 2003, 348:721-726.
12. Horng S and Grady C. Misunderstanding in clinical research: Distinguishing therapeutic misconception, therapeutic misestimation, and therapeutic optimism. *IRB: Ethics & Human Research*, 2003, 25(1):11-16.

***Transformation of Research***  
**CTSI Novel Clinical and Translational Methodologies**

The specific aims of the CTSI Novel Clinical and Translational Methodologies Core are:

1. To foster the development and dissemination of novel approaches to clinical and translational research, including those that take advantage of the rich infrastructure provided by the existing participant, clinical, and translational cores at the University of Pittsburgh and University of Pittsburgh Medical Centre (UPMC);
2. To provide a mechanism by which the use of new approaches, technologies, and methods is promoted within the institution.

In the initial years, the CTSI the Novel Clinical and Translational Methodologies Core will support two important projects that have the potential to have great impact on the clinical and translational research enterprise. These projects, development of an institutional electronic Research Subject Registry and establishment of the CTSI/Carnegie Mellon University/Intel Diamond Collaborative Innovation Center, will be funded for the first two and three years of the CTSI, respectively. In subsequent years, the Novel Clinical and Translational Methodologies Core will solicit applications for awards to develop innovative methodologies that will have a high impact on the clinical and translational research enterprise.

**BACKGROUND**

One of the driving forces for the NIH Roadmap, as stated in the “Overview of the NIH Roadmap,” is the recognition that “[o]ver the years, clinical research that helps discover mechanisms of disease, prevention, diagnosis, or treatment has become more difficult to conduct. Yet the exciting discoveries we are currently making require us to conduct even more efficiently the complex clinical studies needed to make rapid medical progress, and to further inform our basic science efforts. This is undoubtedly the most challenging, but critically important, area identified through the NIH roadmap process.” In the CTSA Request for Application [RFA-RM-06-002]<sup>2</sup>, there is specific recognition that the “NIH has supported the conduct of translational and clinical research through multiple separate programs ... [but that] these investments, however, fall short of recognizing the important linkages between these resources.” Implicit in these statements is the need (1) to develop novel methodologies, approaches, and technologies that, while most immediately focused on a single area, have wide impact on the broader translational and clinical enterprise; and (2) to develop novel clinical and translational methodologies, approaches, and technologies that are focused on facilitating the linkage of data and concepts from a wealth of sources.

The on-line dictionary *Dictionary.com*<sup>3</sup> defines novel as “[s]trikingly new, unusual, or different.” In the context of the Roadmap goals, the most relevant part of this definition is the word “strikingly.” Incremental changes, while valuable when integrated over time, are not what is needed; one either needs to think outside the box or, at a minimum, expand the box in which one is sitting. That is, an effort may be novel not only because it is unique or previously unheard of, but also because it is undertaken on a scale or at a level of complexity that had previously not be tried. Thus, integral to the University of Pittsburgh’s proposed CTSI are a number of activities that are novel because of the scale of the approach. Most exemplary of this is the entire bioinformatics foundation of the CTSI. Another illustrative example, as described elsewhere in this application, is the effort to make the research cores that are extant on the University of Pittsburgh and UPMC campuses accessible to a broader spectrum of investigators than is currently the case. These individual research cores were developed through the initiative and creativity of investigators who had the foresight to recognize the value in a core resource; these cores thus represent the success, energy, and enterprise that has allowed the University of Pittsburgh to rise to its current position as one of the country’s leading research universities. Broad coordination of these cores clearly offers new opportunities for cost-efficiency and expanded access, and yet such coordination could also stifle the individual or group initiative that was key to their development and that is key to the research. As with concepts described throughout this CTSI application, any novel approach must achieve balance between central and distributed processes, while maintaining a sensitivity to the unique culture of an academic health center. Thus, underlying the CTSI programs, as exemplified with the coordination of the core resources, will be an effort to evolve the culture from one that recognizes and rewards an individual primarily, if not solely, on his or her individual

achievements to one in which, there is enhanced recognition, by both the individual and the system, of the value – indeed, the critical importance – of “owning” part of the process, rather than the entirety.

### **Novel approaches and technologies at the University of Pittsburgh**

Engaging in novel means of advancing the clinical and translational research enterprise is not a new concept at the University of Pittsburgh. The examples that follow illustrate some of the approaches that are already in place.

- A group of statistical geneticists, molecular geneticists, and bioinformaticians, led by Dr. Michael Barmada from the Graduate School of Public Health, have recently formed a working group in partnership with a database company, MAYA<sup>4</sup>, to develop a highly scalable, flexible, and distributed information system that can effectively incorporate genetic and genomic databases (including those supported by the National Center for Biotechnology Information) with genotyping and phenotyping data. The goal is to facilitate disease gene discovery and determine attributable risks for large populations.
- Ongoing development also includes new phenotyping methods that are more objective and quantifiable than previous methods, the development of genomic, proteomic, and metabolomic markers for detecting disease, and monitoring disease activities through markers of acute and chronic inflammation (Drs. Michael Lotze and Mitchell Fink). Several groups at the University of Pittsburgh Cancer Institute are using genomic and proteomic profiling of tumors to predict prognoses and to guide future therapies.
- Investigators in the School of Medicine (Drs. David Gur and D.P. Chakraborty) and in the Graduate School of Public Health (Dr. Howard Rockette) are conducting research on clinical trial designs, incorporating innovative ways of adapting analysis of receiver operating characteristics (ROC) to continuous disease states and addressing the topographic aspects of diagnostic methods. Radiologists are integrating spatial concepts into ROC analyses to improve imaging technology capabilities, and biostatisticians and other investigators, led by Dr. Rockette, are exploring ways to modify ROC to describe the ability of a diagnostic detection method to assess diagnosis over a continuum of disease severity, such as diabetic retinopathy.
- Investigators in the School of Medicine (Drs. Robert Branch, Marjorie Romkes) and the Graduate School of Public Health (Dr. Bruce Pitt) are engaged in studies of predictive toxicology in human populations with a goal to identify common genetic variants that affect bioavailability, receptor interaction, and drug metabolism, both for purposes of developing patient-targeted medications and for understanding risks associated with environmental exposures.
- Investigators from the School of Engineering and the School of Medicine, led by Dr. Harvey Borovetz and Dr. Robert Kormos, respectively, are working to develop a personal computer-based Home Monitoring Unit (HMU) to monitor data from heart failure patients with permanently implanted Ventricle Assist Devices (VAD). Current HMU protocols work only with VADs that have been implanted temporarily (i.e., as a bridge-to-cardiac transplant).
- An investigator in the School of Nursing (Dr. Lora Burke) is leading an NIH-study to assess the utility of interactive personal digital assistants (PDAs) in comparison to traditionally-used personal diaries during behavioral weight-loss treatment programs.

While these examples illustrate creative approaches to important issues in medicine and medical practice, the applicability of their success will be, at least initially, narrow in scope. Just as the CTSI sponsored research into novel methodologies will have potentially far-reaching, revolutionary impact, so too do other existing research programs at the University of Pittsburgh Academic Health Center.

Investigators at the University of Pittsburgh Academic Health Center have a track record of developing and launching new interdisciplinary programs that address critical issues in human health. Among the areas in which interdisciplinary research questions are being actively pursued are pain and pain management; the application of computational biology and modeling to complex clinical problems; novel approaches to infectious disease identification, vaccination and eradication; the emerging role of so-called endogenous danger signals that are associated with cellular and tissue damage or injury; and the broadening understanding of inflammatory mechanisms in disease. The efforts in these areas are not in name only. Note, for example, the creation, under the auspices of the Senior Vice Chancellor for the Health Sciences and with support from the President of the UPMC Health System, of the Center for Vaccine Research and the Pittsburgh Comprehensive Pain Center.

The integrated efforts to understand inflammation and the disease processes to which it contributes of several faculty who are located in various departments and schools is a good illustration of the commitment that the

University has to innovative and interdisciplinary translational research. Broadly considered, inflammation – asthma, allergy, autoimmunity, transplantation rejection, cancer in adults, sepsis, emerging infectious diseases (whether natural or the result of bioterrorism), trauma, neurodegenerative diseases, obesity, and atherosclerosis, along with the less well-defined effects of aging – afflicts, or will afflict, all 300 million Americans. The University’s collaborative research program in inflammation leverages a broad and deep expertise in various aspects of inflammation in an effort to establish new paradigms for the diagnosis, study, and treatment of Inflammatory Disorders (IDs). Ultimately, these efforts will lead to improved quality of life for the millions of people who are currently, or will be, afflicted with these conditions. This will be achieved through (1) basic research to understand the genetic and immunologic basis of IDs; (2) clinical research leading to the development of new preventative strategies and therapies; (3) a reduction of barriers among individual disciplines; (4) change in paradigms of clinical practice using existing and emerging immunologic therapies; and (5) development of innovative approaches for student, patient, and physician education.

Classically, the term inflammation was used in the past to denote the pathologic reaction whereby fluid and circulating white blood cells accumulate in extravascular tissues in the initial response to injury or infection. As it is currently used, the term “inflammation” connotes not only localized effects, such as edema, hyperemia, and leukocytic infiltration, but also systemic phenomena such as fever and increased synthesis of certain acute-phase proteins. The inflammatory response is closely interrelated with the processes of healing and wound repair. Indeed, healing is impossible in the absence of inflammation. Importantly, inflammation is a complex process that encompasses both positive and negative feedback loops. It is fundamentally a protective response that has evolved to permit multicellular organisms to rapidly recruit circulating stem cells and inflammatory cells, assess and respond to the presence of pathogens, and rid themselves of injurious agents<sup>5</sup>. Recruited myeloid and lymphoid cells coordinately identify and eliminate effete or stressed cells and remove necrotic cells and cellular debris to enable repair of damaged tissues and organs. However, the mechanisms used to kill invading microorganisms and/or to ingest and destroy devitalized cells as part of the inflammatory response can also be injurious to normal tissues<sup>6</sup>. Thus, excessive or poorly regulated inflammation is a major pathogenic mechanism that underlies numerous acute and chronic diseases, including sepsis, neurodegenerative disorders (such as amyotrophic lateral sclerosis), multiple sclerosis, atherosclerotic disease and resultant stroke, myocardial infarction, and congestive heart failure, acute respiratory distress syndrome (ARDS), asthma, type I diabetes mellitus, inflammatory bowel disease (Crohn’s disease and chronic ulcerative colitis), obesity, psoriasis, rheumatoid arthritis, graft-versus-host disease (after bone marrow transplantation), and cancer. The inflammatory response also plays a key role in the development of complications following major surgical procedures (e.g., extensive ablative operations for cancer, solid organ transplantation, and cardiopulmonary bypass surgery) or accidental trauma. Organ dysfunction and death caused by many “emerging diseases,” including the Ebola and Marburg hemorrhagic fevers, severe acute respiratory syndrome (SARS), and avian influenza, are directly related to cellular injury caused by dysregulated inflammatory and reparative pathways.

Despite the importance of inflammation in virtually all aspects of medicine, remarkably few therapeutic modalities are available to clinicians to modulate this pathophysiological process. Many widely-used classes of anti-inflammatory drugs, such as aspirin, corticosteroids, or non-steroidal anti-inflammatory agents (NSAIDs), were introduced into practice more than 50 years ago. Some newer agents, such as cyclooxygenase II inhibitors, monoclonal antibodies against the cytokine tumor necrosis factor- $\alpha$  (TNF) or to adhesion molecules/integrins important for cellular recruitment and traffic have been approved for clinical use in the past few years. However, these drugs are far from ideal, because they are very expensive, are plagued by unfavorable side-effects, and often require parenteral injection (even for the treatment of chronic conditions, such as rheumatoid arthritis). Clinicians and scientists use different terms to measure and modify fundamentally common processes, creating a lack of synergy and efficacy in early detection, prevention, and treatment of these common disorders. Key to unraveling the complexity of inflammation and its diverse therapies are emerging complex systems approaches, with which most clinicians and even basic scientists are unfamiliar. *The University of Pittsburgh Academic Health Center has established a highly interactive group of clinicians and scientists to drive interdisciplinary understanding, and future clinical management, of inflammation. This interdisciplinary group will form the foundation for planning the development of an institutional Inflammation Center of Excellence.*

As stated in the NIH Roadmap documentation, the “clinical research workforce must be large enough to facilitate bench-to-bedside research, the phased testing of approaches from small to large studies and the translation of proven concepts into medical practice *at the community level* [italics added].” Further, the Roadmap recognizes the need to engage a diverse set of communities – a diversity of populations – in clinical

research as both research subjects and as advocates for clinical research<sup>8</sup>. Thus, engaging the *community* takes on two critical meanings: (1) the critical need to bring community-based medical practitioners into both the clinical research enterprise and into the enterprise that translates clinical research into clinical care; and (2) the critical need to bring the general population, in all of its diversity, into partnership with the clinical research and clinical practice enterprises.

With the UPMC Health System being one of the major health care providers in Western Pennsylvania (19 hospitals; >350 outpatient sites; 3 million outpatient visits/year; 45% market share), the set of potential research subjects who might be engaged in the University's clinical research enterprise is huge. The Health System serves one of the largest rural populations in the United States, as well as both urban and rural communities with strong ethnic and racial identities, including a number of groups that have traditionally been subject to significant disparities in terms of health care access and utilization. While by no means as comprehensive as is ultimately needed, outreach to these communities is an important part of ongoing activities. In particular, novel approaches for engaging some of these communities are under the auspices of the University's Center for Minority Health (CMH), centered in the Graduate School of Public Health. The CMH outreach program, led by Dr. Stephen Thomas, has introduced health care information in nontraditional venues such as beauty salons and barbershops in communities that have been historically distrustful and alienated from traditional healthcare modalities. The importance of church leaders and local business leaders in effecting change within communities is specifically recognized within these outreach programs.

Clearly, one of the strengths that the University of Pittsburgh can bring to bear on improving the clinical (and translational) research enterprise is its partnership with the University of Pittsburgh Medical Center. This partnership will be critical to the conceptual development and eventual implementation of many of the ideas developed and explored under the CTSI activities into Novel Clinical and Translational Methodologies. UPMC has recently established a new office, the Office of Contracts, Grants, and Intellectual Property. A key driving force for the establishment of this office was the recognition that in the evolving relationship between the University and UPMC, there is a critical role for both in clinical research and in translational research. In this regard, the partnership between the two institutions is cemented by the fact that the UPMC vice president in charge of this new office, Dr. Barbara Barnes, is also the University of Pittsburgh's Assistant Vice Chancellor for Continuing Education, Health Sciences. The Chief Medical Officer for UPMC, Dr. Loren Roth, is the University's Associate Senior Vice Chancellor for the Health Sciences.

It is worth noting that the research studies discussed above arose directly from the interests and expertise of investigators who joined in partnership with other investigators with related interests to pursue the relevant research. Such partnering is a hallmark of the University of Pittsburgh, and it will continue to thrive in the rich environment provided by the University of Pittsburgh CTSI. However, as noted, the concept of novel methodologies is multi-dimensional, and the University of Pittsburgh CTSI will foster a range of activities that will push the frontiers of the approaches used in clinical and translational research. In particular, the CTSI will sponsor novel research that will have impact on a broad spectrum of clinical and translational applications.

## **CORE DESIGN and METHODS**

### **Institutional Research Subject Registry Development: Years One and Two**

Ultimately, the CTSI will solicit ideas for the development of novel methodologies from a range of sources, as discussed below. However, during years one and two, the CTSI will develop a novel methodology that will overcome a major barrier to the performance of research by nearly all clinical, and many translational, researchers. It is clear from a myriad discussions across campus that one of the key impediments to the successful completion of many clinical research programs is the inherent difficulty of adequate human subject recruitments. Recruitment meets all of the criteria described above for requiring novel clinical methodology. Improvements in recruitment will have wide impact on the broader translational and clinical enterprise. Successful recruitment will allow investigators to take advantage of the linkage of data and concepts from a wealth of sources. Traditional recruitment activities are inefficient to the degree that it has become necessary to think outside the box or to expand the box in which one is sitting. The range of clinical research activities for which subject recruitment is needed continues to expand. When coupled with the regulatory demands and enhanced exclusion requirements for studies, recruitment must be undertaken on a scale or at a level of complexity that has previously not been tried. Thus, one of the two initial forays into novel clinical and translational methodologies to be supported under the CTSI will focus on human subject recruitment.



Research subject recruitment for clinical studies (both clinical trials and longitudinal research) has reached a crisis stage in the United States. Despite the efforts of individuals such as Lance Armstrong in bringing an awareness about clinical research to the general public<sup>9-10</sup>, the percentage of eligible individuals who participate in clinical studies is extremely low<sup>11-12</sup>. The problem has been exacerbated by increasing pressure on clinicians to see more patients, to conform to more stringent practice guidelines, and to spend less time per patient; this frequently results in patients not being informed about opportunities to participate in research studies. At the same time, the public perception of research has been affected by the occasional, but sensational, reports of research malfeasance and of individuals harmed by participation in such research.

Many of the clinical investigators at the University of Pittsburgh report that the primary barrier to conducting successful clinical studies is the challenge of meeting recruitment targets in a cost- and time-effective manner. The recent changes in regulations for protecting personal health information have complicated the recruitment process by placing limits as to whom, and as to how, the task of identifying prospective subjects can be delegated. One avenue for enhancing participation in clinical research, especially in clinical trials, that is gaining increasing popularity is the creation of centralized, institution-wide research registries. Such registries obviate the need for obtaining individual, targeted consent for each discrete screening activity, while staying within the confines of HIPAA regulations. A patient is often asked during the initial visit with a physician to provide revocable consent to have at least a portion of his or her medical information accessible for screening for potential participation in clinical studies; such consent and the referenced clinical data form the basis for these centralized registries. Such registries are necessarily incomplete, in that many individuals are willing to provide screening access to only a portion of their medical records; that is, they are willing to be contacted about participation in clinical trials only for specified medical conditions. Further complicating use of such a registry is that potential subjects wish to be contacted by different means (*e.g.*, mail, telephone, e-mail); this may necessitate a time-consuming process for establishing patient participation. Perhaps the greatest challenge in building and using a centralized registry is the need to manage complex data that cover tens of thousands, if not hundreds of thousands, of individuals. While centralized research registries clearly are tremendous assets for conducting clinical research, they are far from sufficiently robust to be maximally useful to clinical investigators.

As one of its first forays into the development of a novel methodology that has the potential to transform the University of Pittsburgh Academic Health Center research enterprise, the CTSI will design, develop, and implement an institutional research subject registry. This registry will be embedded in the UPMC's electronic health record (EHR) systems and will be implemented in UPMC's 350 outpatient practice locations and 19 hospitals. It will have enhanced value for patients (potential research subjects) by providing opportunities for health and wellness education, as well as the opportunity for potential improvement in individual health through participating in state-of-the-art clinical research. In addition to these potential benefits for patients, the registry will provide increased utility for clinical investigators, relative to more traditional domain-specific registries. Establishment of this registry as the first CTSI-supported Novel Methodology is expected to take two years, with CTSI funding at a level of \$\_\_\_\_\_ per year. In addition to the CTSI-allocated budget for the development of this registry, the Senior Vice Chancellor for the Health Sciences will provide \$\_\_\_\_\_ for staff and technology needs. The UPMC Health System will provide staff and resources for the continued development of the interoperability of the EHR systems and the registry.

The development of this registry will involve the integration of, and incorporation into, the greater than 50 EHR systems that exist across the UPMC facilities. Development will also require linkages to web-based patient portals that currently exist to facilitate patient access to state-of-the-art health and research information, physician and clinical staff participation, and educational programs targeted at both potential subjects and at clinical providers. These elements must be included in the CTSI registry in ways that respect the privacy and individual sensitivities of the community of potential subjects and that minimize interruption of clinical office workflow. An integrated recruitment registry program is not merely population of an established database; it is a coordinated effort involving web-based tools, database systems, integration with clinical informatics tools, and a new set of management and educational processes to ensure acceptability, access, and ethical compliance. Accordingly, the development of the CTSI registry will require expertise in and coordination across several CTSI key functions: Center for Clinical and Translational Informatics, Community PARTners Research, Participant and Clinical Interactions Resources, Regulatory Knowledge and Support, and Research Education, Training and Career Development.

## **Development of the CTSI Research Registry**

The primary objective of this registry is to identify and recruit UPMC patients and volunteers from every UPMC point-of-service location (3,000,000 outpatient visits and greater than 150,000 inpatient hospitalizations per year) who may be eligible to participate in ongoing CTSI clinical and translational research studies.

**Justification:** Formal surveys of patients have revealed that an overwhelming majority are willing to allow their medical record information to be used for research purposes provided that they are first asked for their permission for such use and that safeguards are established to protect the privacy of this information<sup>13-14</sup>. The University of Pittsburgh IRB currently grants waivers of written informed consent (and, when applicable, HIPAA authorization) for the use of identifiable medical record information for retrospective research studies and for the identification of individuals who may be eligible to participate in ongoing, approved clinical research studies. Such waivers are granted provided that the individuals who access the medical information for these purposes are involved directly in the care of the respective patients. While this approach serves to protect the privacy of the patients' medical information by limiting access to health care staff who would already have knowledge of the information, it assumes *a priori* that the respective patients would agree to permit the use of their medical information for research purposes. In addition, there are practical and ethical questions associated with attempting to define the scope of being "involved directly in the care of the respective patients." For example, in a medical clinic environment, should all health care staff of the clinic be considered to be involved directly in the care of all clinic patients? Should a health care staff member working within a certain clinic environment be permitted to access, for research purposes, the medical record information of patients who were seen in the that clinic prior to his/her date of hire?

For investigators who desire access to certain medical record information but who are not involved directly in the care of the respective patients, the University IRB frequently recommends the use of an "honest broker" process. With this process, an individual (i.e., honest broker) who normally has access to the respective patients' medical record information by virtue of his/her job responsibilities collects the desired information and de-identifies it prior to providing the information to the investigator. The honest broker may assign re-identification code numbers to the medical record information given to the investigator, but the data linking these code numbers to the corresponding patient identities are retained by the honest broker. For retrospective research studies, this approach will typically suffice, provided that the extent of de-identification required by the HIPAA regulations permits the retention of sufficient information to conduct the research. However, the use of this approach for the identification of individuals who may be eligible to participate in ongoing clinical research studies and their subsequent recruitment is cumbersome and inefficient. In this case, after identifying the coded medical information of potentially eligible patients, the investigator needs to return to the honest broker. Using the re-identification code, the honest broker then identifies the potentially eligible patients and, to avoid a "cold-calling" scenario, provides this information to a physician or health care worker involved directly in the care of the patient (i.e., assuming that the latter criteria does not apply to the honest broker). This physician or health care worker subsequently contacts the potentially eligible patient to ascertain his/her interest in study participation. While feasible, the ever-increasing demands being placed on the time of health care staff render it difficult for investigators to recruit research subjects using this approach.

The CTSI Research Registry will serve as a mechanism that will respect the rights and welfare of the patients while promoting the research efforts of CTSI investigators. The CTSI will accomplish this by using informatics to obtain prospectively the written permission of UPMC patients throughout the health system to use their medical record information for the purpose of recruitment into research studies.

**Registry Design and Methods:** The CTSI Research Registry will require the development of software that interacts with (1) existing electronic patient registration systems at UPMC; (2) the recently developed "Central Data Repository (CDR)" that provides interoperability among the various EHR systems at UPMC; and (3) a database of all CTSI research studies that includes inclusion and exclusion criteria. This approach is parallel to a UPMC clinical quality assurance initiative that prompted the development of the CDR. Once developed, the registry will function as follows:

1. Upon outpatient registration in a UPMC-affiliated healthcare setting (e.g., one of 350 outpatient offices), UPMC patients will be asked to provide their written permission to participate in the Research Registry. This will be accomplished by reconfiguration of the electronic registration system to identify automatically patients who have not previously been approached to participate or who have been approached but have neither consented nor declined to participate. The system will print an IRB- approved consent form and informational materials that will be given to the patient by trained clinical staff. Possible outcomes of this

interaction are: (a) the patient consents and will be entered in the registration system as a registry participant; (b) the patient requests additional information, which will prompt an electronic notification to CTSI staff; (c) the patient declines; or (d) none-of-the above, which will result in an electronic tag in the EHR that will prompt re-initiation of the process at the next visit.

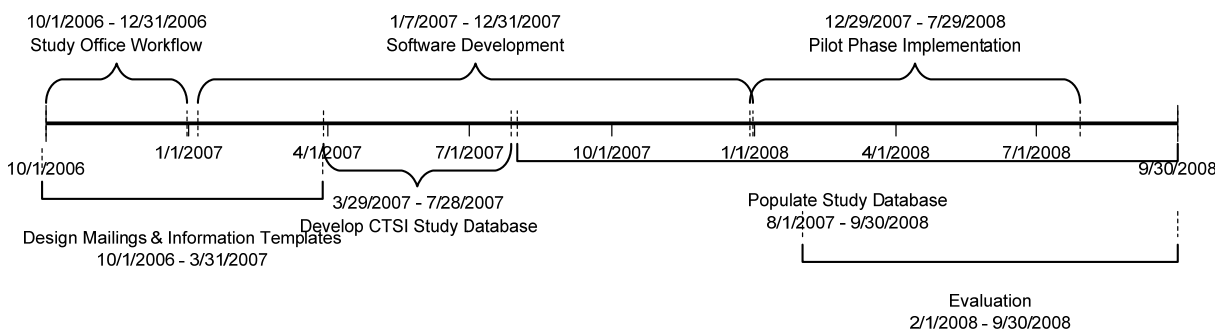
2. After providing consent, all medical records that pertain to each consenting participant and that are stored in the greater than 50 UPMC EHR systems will be collected by the CDR. This information will be queried by the CTSI research study database daily to match patients and relevant CTSI studies. Note: The CDR will be stored on a UPMC server that has privacy protections (e.g., firewalls, locked rooms, encryption) that are used by UPMC clinical information systems. These clinical systems afford HIPAA-required privacy protection in accordance with all governing laws.
3. Registry participants will receive an initial mailing from the CTSI registry office. This computer-generated mailing will provide general information about clinical research to enhance the participant's understanding of clinical research (*i.e.*, to develop a "research-informed patient"), clinical research vignettes to demonstrate the benefits of participating in research, general wellness information and information related to a health issue that may have been identified in his/her medical profile, and a listing of research studies that are relevant to his/her health. Participants will receive ongoing information about specific research studies that are pertinent to their health based on their demographic and medical profiles in the EHR systems. These customized mailings will be followed up by telephone contact by the CTSI registry office staff. In these mailings and telephone calls, participants will be given contact information for investigators or coordinators who are responsible for specific studies and encouraged to contact these study personnel to obtain additional study-specific information. In addition, mailings will contain forms that participants can send to the registry office to grant permission to investigators for selected studies to initiate contact to provide additional information.

Linkages between the Central Data Repository (CDR) and a research study database provides opportunities to address other important issues that are relevant to clinical and translational research. The CTSI will implement an institutional requirement that every UPMC patient who is enrolled in any AHC research study be identified in an electronic database that is linked to the CDR (please note, IRB consents will list this requirement). The CDR will, in turn, be linked to the Clinical Trials Management Application (CTMA, see CTSI Center for Clinical and Translational Informatics) for the purpose of fiscal oversight. Specifically, the interaction between CTMA, which will identify research-related procedures to be performed in each study, and the CDR, which will route the CTMA to electronic clinical billing records for each research participant/ patient, will reconcile research vs. clinical billing. A second example is the use of the CDR to capture electronically all outpatient visits and hospitalizations of study participants to improve the capture of adverse and serious adverse events.

#### CTSI Research Registry Evaluation process

The CTSI registry office will query the patient registration system to determine the number of patients registered daily at each outpatient clinical site and the number of patients who consented or declined to participate. Participant tracking will include determinations of whether mailings were sent, response to mailings, and enrollment in studies. The results of this evaluation will provide guidance for dynamic modifications in the registry to optimize recruitment of clinical patients into research studies.

#### Proposed Timeline for Implementation of the CTSI Research Registry



### Summary of the CTSI Research Registry

This research registry is a novel method to recruit research subjects because (1) it will recruit patients at greater than 350 outpatient offices in 29 counties using Information Technology; (2) it will merge clinical records from greater than 50 EHR systems with a database of nearly 6,000 ongoing clinical and translational studies to identify potential research subjects; and (3) it will result in the development of an informatics system that is potentially exportable to other CTSA sites to link de-identified research subject databases throughout the United States.

### **Diamond Collaborative Innovation Center: Years One to Three**

The partnership between the University of Pittsburgh, Carnegie Mellon University, and Intel Research Pittsburgh provides a unique opportunity to explore a second novel methodology that has the potential to impact translational and clinical research, as well as clinical practice. A second novel methodologies to be sponsored by the CTSI during the initial years is Diamond software, the potential medical applications of which will be explored with the support of the Novel Clinical and Translational Methodologies core. The institutional and industry collaboration represented by this activity provides a model for the type of interactions with industry that will be incorporated into the CTSI. The impetus for the development of Diamond and its potential for medical application are described below.

### Moving Beyond Text Searching to Image Searching: Data Driven Searches with Diamond

How does one find a few vaguely-specified items in many terabytes or petabytes of complex and loosely-structured data such as digital photographs, video streams, CAT scans, X-rays, or other imaging data that are distributed over many Intranet and Internet sites? If the data have already been indexed for the query being posed, the solution is well-understood. This is exactly what search engines such as Google™ do. Unfortunately, a suitable index is often not available, and a user has no choice but to perform an exhaustive search over the entire volume of data. Although attributes such as hospital, physician, date, or other meta-data can restrict the search space, the user is still left with an enormous number of items to examine.

Enabling efficient interactive distributed searches of such data could enable a domain expert, *e.g.*, a radiologist, pathologist, endoscopist, microscopist, or cytologist, to guide a search toward discovery of a small set of relevant items buried in huge distributed collections of imaging data. It would also enable interactive data exploration by medical researchers and diagnosticians, possibly leading to deep domain-specific insights and enhanced diagnostic ability. From a broader perspective, it would empower the medical community with the ability to “play” with large volumes of imaging data at Internet scale and to easily answer “what if” questions. Just as the invention of the spreadsheet in the early days of personal computing improved decision-making by the business community, efficient interactive search of complex, non-indexed, distributed imaging data can be foreseen as a fundamental new tool that could revolutionize discovery and decision-making in the health sciences.

Diamond is an open-source software system jointly created by Intel Research and Carnegie Mellon University to provide this capability<sup>15</sup>. It embodies new software architecture for rapidly scanning large volumes of distributed data and filtering that data with domain-specific software. This is the critical technical breakthrough needed for creating the capabilities discussed in the previous paragraph. Central to the Diamond architecture is the concept of early discard: the ability to reject irrelevant data items very close to their point of storage, thus incurring low data transmission overhead. This architecture can be mapped to a variety of storage back-ends such as SANs (storage area networks), blade servers on LANs (local area networks), Internet servers, and distributed file systems.

### Potential Application of Diamond to Clinical and Translational Research: Interactive Search-Assisted Diagnosis (ISAD)

Under the novel methodologies core, a new approach to medical diagnosis called Interactive Search-Assisted Diagnosis (ISAD) in the context of evaluating breast lesions depicted on mammograms and pathology images will be investigated. If successful, this approach should have widespread applicability to many other diagnostic contexts that involve extensive use of imaging. The project will build on the experience of University of Pittsburgh Academic Health Center researchers in using ISAD for diagnosing breast lesions by developing collaborations with other clinicians and researchers for broadening the usage context of ISAD. The software support for this new search capability is embodied in Diamond. Specifically, the development of several novel ISAD tools based on Diamond for processing digital mammograms, breast core biopsies, fine needle aspiration

(FNA) samples, and excisional biopsies of breast masses is proposed. These ISAD tools will be applied to both pathological and radiographic images. The feasibility of applying and integrating Diamond with ISAD tools or schemes for improving the detection and diagnosis of cancers depicted on a variety of medical images will be tested.

The source code for Diamond is publicly available for download at <http://diamond.cs.cmu.edu>. The Diamond architecture makes a clean separation between the domain-specific and domain-independent aspects of distributed large-scale search. Examples of domain-specific aspects include algorithms for interpretation of images, similarity detection, notation for relevance feedback, and a graphical user interface (GUI) that is customized to the task of mammogram interpretation. Examples of domain-independent aspects include self-tuning to accommodate large variation in the speed and storage capacity of different servers, dynamic adaptation to Internet bandwidth and server load, caching and efficient reuse of results from previous searches, and dynamic adaptation to variation in the computational demands of diverse search queries and data content. The research proposed here will create and validate Diamond applications that embody the domain-specific knowledge relevant to diagnosis of breast lesions using mammograms and pathology images. The goal of this study is to search, efficiently and effectively, for (identify) the suspected breast mass regions depicted on either mammograms or pathological images that are visually similar to the queried mass region from two large and diverse reference libraries established at the Departments of Radiology and Pathology, respectively.

The two specific aims of this Novel Clinical and Translational Methodologies project are as follows:

1. An ISAD scheme based on the collaborative work that has already been performed will be investigated. This work will be expanded to so-called “whole slide images (WSI)”, also known as virtual slides (VS), for improved diagnosis and reduced turnaround time.
2. An interactive image matching and pattern recognition scheme based on Diamond will be developed and integrated into an ICAD system that is under development at the Imaging Research Center of the Department of Radiology at the University of Pittsburgh School of Medicine. Specifically, a new computer matching scheme that uses Diamond as an optimization tool to improve identification of visually-similar breast masses depicted on digitized mammograms will be developed and tested. Image-based similarity measures is a difficult but important task in the development and application of an ISAD system that aims to help radiologists detect subtle masses and classify them into malignant and benign.

After appropriate evaluation of effectiveness, expanded efforts to other domains such as cytology, endoscopy, and more general applications in pathology will be explored. Furthermore, engagement of predoctoral students, residents, fellows, and faculty in suitable mentored application of these new tools will be carried out through the Research, Education, Training and Career Development Core.

### **Novel Clinical and Translational Methodologies, Years Three and Beyond**

The decision to focus initial novel methodology activities on the development of a multi-functional research registry arose from a specific need articulated by myriad investigators from across the spectrum of clinical researchers at the University of Pittsburgh. The decision to explore the use of Diamond in medical applications arose from the unique opportunity afforded by the partnership between the University of Pittsburgh Academic Health Center, Carnegie Mellon University, and Intel Research. In future years, a more structured process will be used to identify areas for which break-through methodologies are needed and to solicit proposals for research activities directed towards these needs.

Since the goal of the novel methodologies program is to develop processes that have broad applicability to at least some aspect of translational and/or clinical research and that have potential for applications to a large group of CTSI members, any decision as to area to pursue will be vetted by the CTSI Steering Committee, the CTSI Executive Committee, and the multidisciplinary Internal Advisory Committee. The combined perspectives represented by these three groups are comprehensive as to the goals of the CTSI and as to the ongoing and planned activities to achieve these goals. Thus, these committees will be able to determine the congruence of any proposed novel methodology with the CTSI mission.

How will new programs for novel methodology development be proposed? Just as the articulation of the need for a robust research registry emerged from discussions with the spectrum of clinical investigators whose

research was stymied by the inability to attract adequate subject populations, especially under the current regulatory climate, it is likely that other areas of need will surface from such grassroots discussions. These discussions will include focus groups of investigators and coordinators and will take place as part of activities during the annual CTSI “Synergies in Health Research Day.” Any idea that surface through this mechanism will be required to undergo the more formal process, described below, that solicits concepts for consideration.

Two years ago, the University of Pittsburgh, through the University Research Council that reports to the Office of the Provost, implemented a Multidisciplinary Small Grant Program. “The program encourages faculty with different skills and training to address complex problems that span the humanities, social sciences, engineering, physical sciences, and/or the biological and health sciences<sup>16</sup>.” Paralleling this concept, the NIH Roadmap defines interdisciplinary research as that which “integrates the analytical strengths of two or more often disparate scientific disciplines to create a new hybrid discipline. By engaging seemingly unrelated disciplines, traditional gaps in terminology, approach, and methodology might be gradually eliminated<sup>17</sup>.” The development of novel research methodologies that, by definition, advance the state of the art, will require an interdisciplinary approach, and the Multidisciplinary Small Grant Program offers a model for solicitation of concepts for novel research methodologies. To wit, two page white papers are requested that “describe the proposed project, paying particular attention to the novelty of the project, its multidisciplinary nature, and its potential for future development. The white paper also should outline the skills that each investigator contributes to the project and how this combination of skills will ensure good progress toward the investigators’ objectives.” These white papers are reviewed by the members of the University Research Council, and full, ten page applications are requested from the authors of those applications that are deemed as highly responsive to the solicitation. The review criteria for the full applications include assessment of “exceptional creativity, potential for ground-breaking discovery, prospects for making seminal research and scholarly advances.”

With appropriate modifications, such a procedure will be followed for the CTSI novel methodologies solicitations. Three page white papers will be solicited that clearly articulate the need(s) that cannot be met by extant methodologies. Champions for any ideas that have surfaced through grassroots discussions will be contacted and invited to submit white papers in response to the novel solicitation. These white papers will be reviewed by CTSI Steering Committee, the CTSI Executive Committee, and the Internal Advisory Committee. The authors of the three white papers that are deemed as most clearly addressing critical needs will be invited to submit full applications. These full applications will be 15 pages in length, plus supporting documentation. The full applications will be reviewed by a subcommittee comprised of senior CTSI members who will rank them according to importance and urgency. The final decision as to which program to support will be made by the CTSI Steering Committee.

As noted in the Pilot and Collaborative Translational and Clinical Studies section of this application, the Office of Research, Health Sciences will be responsible for the CTSI pilot program, and the OORHS will have in place a robust process for managing a grant solicitation and the subsequent review process. Thus, the OORHS will assume the lead responsibility for the practical aspects of the novel methodologies solicitation. In Year 03, funding for this program will be \$ \_\_\_\_, with total funding in Years 04 and 05 reaching \$ \_\_\_\_ per year. Each supported project will receive up to two years of support. It is worth noting that it is historically the case that research programs or research methodology developments that have broad potential applicability have also been supported, at least in kind, by the Office of the Senior Vice Chancellor for the Health Sciences, often in concert with support from the Offices of the Chairs of Clinical Departments. It is thus likely that CTSI funds will be leveraged against institutional support.

### **Evaluation and Outcomes**

The expected outcome of this CTSI core is the development of novel methodologies that have broad potential applicability in the context of translational and clinical research. The proposed research registry will be assessed by its success in enhancing the level of subject recruitment over existing mechanisms for recruitment and by the degree to which it provides “value added services” to clinical investigators. The Diamond Collaborative Innovation Center will be assessed by its success in establishing the utility of the Diamond software for medical image analysis for diagnostic purposes. For details of the evaluation process please see the CTSI Evaluation section of the application.

**Proposed Timeline for Implementation**

Year 1	Year 2	Year 3	Year 4	Year 5
CTSI Research Registry development and rollout (see detailed timeline above)				
Diamond Collaborative Innovation Center funded				
	Midway through years 02, 03, and 04 an RFA will be issued and concepts evaluated for funding in years 03, 04, 05, respectively.			
		Fund novel methodology proposal solicited in year 02		
			Fund novel methodology proposal solicited in year 03	
				Fund novel methodology proposal solicited in year 04

**Transforming the Translational and Clinical Research Enterprises**

As discussed in the overview of the CTSI application, the University of Pittsburgh Academic Health Center has a history of research that has transformed the practice of medicine in such fields as organ transplantation and resuscitation. The focus of the Novel Clinical and Translational Methodologies core is to continue that tradition, but to do so while taking advantage of modern tools, particularly those encompassed by the broad field of information technology, that enable an integration across many disciplines. The two “Novel” projects that will be undertaken initially, the Research Subject Registry and the Diamond Collaborative Innovation Center, each have the potential to revolutionize clinical research and clinical practice. The Registry program will remove what is arguably the major roadblock to the conduct of valuable clinical trials – the inability to recruit an adequate subject base. The Diamond project may revolutionize both the ease of analysis of a given medical image and the ability to correlate findings from a suite of different images, either from a single imaging modality or from different modalities. Similarly, any projects selected for funding through this CTSI core in years three and beyond will, as a selection criterion, have revolutionary potential.

**Literature Cited:**

1. National Institutes of Health. The NIH Roadmap for Medical Research Overview page. Available at: <http://nihroadmap.nih.gov/overview.asp>. Accessed February 28, 2006.
2. National Institutes of Health. Institutional Clinical and Translational Science Award page. Available at: <http://nihroadmap.nih.gov/grants/index.asp>. Accessed January 26, 2006.
3. Dictionary.com. Available at: <http://dictionary.reference.com/>. Accessed February 28, 2006.
4. Maya Viz. About Maya Viz page. Available at: <http://www.mayaviz.com/web/about/about.mtml>. Accessed February 28, 2006.
5. Nathan C. Points of control in inflammation. *Nature*. 2002;420:846-852.
6. Lotze MT, Tracey KJ. High-mobility group box 1 protein (HMGB1): nuclear weapon in the immune arsenal. *Nat Rev Immunol*. 2005;5:331-342.
7. National Institutes of Health. The NIH Roadmap for Medical Research: Re-Engineering the Clinical Research Enterprise Clinical Research Training Overview page. Available at: <http://nihroadmap.nih.gov/clinicalresearch/overview-training.asp>. Accessed February 28, 2006.
8. National Institutes of Health. The NIH Roadmap for Medical Research: Patient Recruitment Core PowerPoint slide page. Available at: [http://nihroadmap.nih.gov/clinicalresearch/rtrc/ppt/294,3,Patent Recruitment Cores](http://nihroadmap.nih.gov/clinicalresearch/rtrc/ppt/294,3,Patent%20Recruitment%20Cores). Accessed February 28, 2006.
9. Lowe J. Lance Armstrong Team Rides for Clinical Trials. *CancerWise™* [serial online]. September 2005 issue.
10. U.S. Senator Bob Bennett (Utah). Bennett and Lance Armstrong Raise Awareness for Cancer Research. Available at: <http://bennett.senate.gov/press/record.cfm?id=224659>. Accessed February 28, 2006.
11. Murthy VH, Krumholz HM, Gross CP. Participation in Cancer Clinical Trials: Race-, Sex-, and Age-Based Disparities. *JAMA* [serial online]. 2004;291:2720-2726. Available from: American Medical Association, Chicago, IL. Accessed February 28, 2006.
12. Comis RL, Miller JD, Aldigé CR, Krebs L, Stoval E. Public Attitudes Toward Participation in Cancer Clinical Trials. *Journal of Clinical Oncology* [serial online]. 2003;21:830-835. Available from: American Society of Clinical Oncology, Alexandria, VA. Accessed March 6, 2006.
13. Kass NE, Natowicz MR, Chandros Hull S, Faden RR, Plantinga L, Gostin LO, Slutsman J. The Use of Medical Records in Research: What Do Patients Want? *Journal of Law, Medicine, & Ethics* [serial online]. 2003;31:429-433. Available from: American Society of Law, Medicine & Ethics, Boston, MA. Accessed March 15, 2006.
14. Willison DJ, Keshavjee K, Nair K, Goldsmith C, Holbrook AM. Patient consent preferences for research use of information in electronic medical records: interview and survey data. *BMJ* [serial online]. 2003;326:373. Available from: The British Medical Association, London, U.K. Accessed March 15, 2006.
15. Huston L, Sukthankar R, Wickremesinghe R, Satyanarayanan M, Ganger GR, Riedel E, Ailamaki A. Diamond: a storage architecture for early discard in interactive search. In: *Proceedings of the 3<sup>rd</sup> USENIX Conference on File Storage Technologies*. San Francisco, CA: 2004.
16. The University of Pittsburgh. University Research Council Multidisciplinary Small Research Grant Program page. Available at: <http://www.pitt.edu/~vpres/URC/programs/Interdisciplinary%20Small%20Grants%20Program%20RFP.pdf>. Accessed February 26, 2006.



17. National Institutes of Health. The NIH Roadmap for Medical Research: Interdisciplinary Research Overview page. Available at: <http://nihroadmap.nih.gov/interdisciplinary/index.asp>. Accessed March 20, 2006.

**Transformation of Research****CTSI Center for Clinical and Translational Informatics (CCTI)**

The goal of the Center for Clinical and Translational Informatics (CCTI) in the Clinical and Translational Science Institute (CTSI) at the University of Pittsburgh is to utilize biomedical informatics to maximize efficient information management and ensure data integration at each step in the "lifecycle" of clinical and translational research projects. This will first be accomplished locally by developing open source tools to allow the CTSI research community to more effectively share and utilize research data. These tools will then be connected via grid computing and shared with other Clinical and Translational Science Award (CTSA) sites nationally. This transformation will be tightly coupled to a comprehensive plan for educating researchers about the utility and value of these tools throughout the lifecycle of clinical and translational research. The following **specific aims for the CCTI** have been defined:

1. **Implement and Maintain Advanced Software Tools and Methodologies.** The most advanced, integrated informatics tools will be developed, implemented, and maintained to support CTSI-sponsored research. These tools will enhance the efficiency of the research projects and address the current unmet need for seamless integration of clinical and research data. This aim will also facilitate the identification of barriers to data flow from both bench-to-bedside and bedside-to-clinical practice settings. Accomplishing this aim will require an advanced informatics plan consisting of several biomedical informatics cores linked to the educational, translational and clinical research, and dissemination missions of the CTSI locally and the CTSA program nationally, particularly those supporting clinical trials, biorepositories, and biomarker development. These tools will serve the project review process, measuring efficiency, and time line adherence and will be focused on quality and productivity. The new CCTI will be CTSI's home for developing modeling strategies, data mining techniques and other areas of innovation in service of translational research through informatics.
2. **Create an Interoperable Grid Computing Environment for CTSI.** "Open source" tools developed by the CCTI will be implemented, supported, and shared with all components of the University of Pittsburgh's CTSI through a core architecture (caCORE) in an interoperable grid (caGRID), using tools developed by the Cancer Biomedical Informatics Grid (caBIG) program of the NCI. This computing grid will allow software developed at the University of Pittsburgh to be migrated to an open source, tightly integrated environment. The software tools described in Specific Aim 1 will be re-engineered to an interoperable infrastructure that can be supported by a grid computing architecture, including the development of robust vocabulary/ontology services and syntactic/semantic networking tools provided by caBIG. This specific aim implies that an advanced architecture for national CTSA sites will be piloted at the University of Pittsburgh during the initial funding period and subsequently be made available to all CTSA sites. Since CTSA sites are expected to share "best practices" and tools among funded sites, an approach for sharing, implementing and maintaining the informatics tools is proposed. The developed infrastructure will be piloted to other national CTSA sites as deemed appropriate by the CTSA Biomedical Informatics Steering Committee.
3. **Facilitate the Development of and Support for CTSI informatics tools through an Online Research Community.** A CTSI Online Research Community (ORC) will be developed as an electronic infrastructure that is expected to transform communication, information sharing, and access to education for the University of Pittsburgh research community and colleagues in the surrounding region. The current lack of transparency of information about research resources, services and scientists is a significant barrier to conceiving and executing complex research projects. A comprehensive, open, easily accessible and user-centered community information resource that incorporates intelligent information routing can help alleviate this barrier. The three core elements of the CTSI ORC are: (1) comprehensive, information-rich directories of people, research interests, projects, services, funding opportunities, and other research-related entities; (2) intelligent information routing that both "pushes" information to and "pulls" information from members of the CTSI community; and (3) education in clinical and translational informatics that is linked to the Clinical Research Scholars and Clinical Research Training Programs and is connected to the training needs of clinical and translational research scientists. Formal training will be provided (Master's and Doctoral), as well as support for the IT training needs of researchers using existing translational informatics tools. More importantly ORC will provide an important tool to connect effectively with and provide information and education widely to community physicians.

**BACKGROUND****Local issues of significance for the CTSA Program.**

The CTSI at the University of Pittsburgh, led by Steven Reis, MD will integrate two GCRCs, one K12, and one K30 program. A major component of this integration effort will be accomplished in partnership with the CCTI, led by Michael J. Becich, MD, PhD, who is a co-director of the CTSI. This integration will require extensive

development, implementation, and coordination of the informatics resources needed to serve all aspects of clinical and translational research at the University of Pittsburgh. Informatics resource coordination by the CCTI is an important component of the research transformation that will occur through the CTSI. This major organizational change is represented by the newly established Department of Biomedical Informatics which is led by Dr. Becich and is strongly supported by the Senior Vice Chancellor for the Health Sciences (see support letter from Dr. Levine) and the Chancellor of the University of Pittsburgh. This new department will be established through the merger of the Center for Biomedical Informatics, the Center for Pathology Informatics, and the Benedum Oncology Informatics Center and will be launched July, 2006. The merger of these three centers and their integration with the GCRC Information Technology Core, along with the clinical and translational research tools already developed by these groups will provide a strong foundation for the CTSI. The new Department, which will house the CCTI, has strong institutional support from the School of Medicine (\$1.9M) for recruitment of new faculty, and has commitments for nearly 12,000 sq feet (available 4/1/06) in addition to the 15,800 sq feet it currently occupies. 40,000 sq feet of new contiguous space will be available in two to four years and will allow for physical integration of all personnel in the current three centers and GCRC Information Technology Core.

The UPMC has a central informatics support organization that manages the clinical and business needs of the entire Academic Health System. This organization, the Information Services Division (ISD) has an annual operation and capital budget of over \$176M. Since 1991, Dr. Becich has directed all of the clinical informatics operations for Pathology (19 hospitals plus overseas operations). In 2001, he also assumed responsibility for all Oncology Informatics operations. The capital and operation budgets for these two UPMC ISD Informatics units total over \$3.8M annually. This span of authority (both tactical and budgetary) will greatly facilitate the goals of the CCTI, including the interoperability that will be required to facilitate comprehensive and standardized support for all clinical and translational research in the CTSI. Evidence of UPMC's support for the integration plan is its formation of a new center called the Center for Strategic Informatics (CSI), which will also be directed by Dr. Becich. The three major roles of this new center are synergistic with the goals of the CCTI and CTSI and will be:

1. To develop and implement a plan for interoperability among clinical applications supporting the electronic medical record systems of UPMC through its central IT group (i.e., ISD). See letter of support from CMO of UPMC (Dr. Roth) and VP for E-Record (Dr. Martich).
2. To be responsible to the University of Pittsburgh's Office of Research for the implementation of a comprehensive plan to support facilitated access to clinical data captured during care delivery, via a robust set of de-identification and honest broker tools developed by Dr. Becich and his collaborators. For more detail see Specific Aim #1.
3. To develop strategic business initiatives with commercial partners that lead to industrial collaborations, sponsored research agreements, and contracts and to the development of an intellectual property portfolio of patents, licenses and royalties for both UPMC and the University of Pittsburgh. (see letter of support from CIO of UPMC, Dan Drawbaugh). See the "CTSI Catalyst Program" section for more detail.

This infrastructure encompassing all six Schools of the Health Sciences, a network of 19 hospitals, over 100 affiliated outpatient offices, and community-based services of the UPMC will greatly facilitate the goals outlined in the proposal that follows. Both the University of Pittsburgh and the University of Pittsburgh Medical Center are heavily invested in and committed to the success of the CCTI, and both have also demonstrated unequivocal and vocal support for Dr. Becich's leadership for this highly integrated endeavor.

### **National Issues of Significance for CTSA Program.**

Informatics research and development activities are increasing significantly in the NIH and other agencies of the Department of Health and Human Services. The NIH Roadmap specifically recognizes informatics as a key component in achieving advances in the understanding of disease and the improvement of health.<sup>1</sup> Indeed, a trans-NIH Informatics Committee (TNIC) has been established to coordinate all informatics activity under the Roadmap. An example of such an activity is the National Electronics Clinical Trials and Research (NECTAR) network, which has been created to enhance the efficiency of clinical research networks through informatics and other technologies, so that investigators will be better able to broaden the scope of their research.<sup>2</sup> A second example is the recently funded cancer Biomedical Informatics Grid (caBIG) project<sup>3,4</sup>, which is coordinated by the National Cancer Institute. caBIG investigators across the U.S. are developing and evaluating informatics tools and networks to support cancer-research groups with the goal of advancing translational research in cancer. A third example is the recent funding of seven National Centers for Biomedical Computing; two of which are focused on translational informatics and a third on biomedical ontology which is critical for integrating clinical and research informatics efforts.<sup>5</sup>

Further evidence of the increasing importance placed by the nation on informatics research and development is Dr. David Brailer's appointment as the first National Health Information Technology Coordinator in May 2004.<sup>6,7</sup> Dr. Brailer's duties as National Coordinator are to execute the actions stated by President George W. Bush in his Executive Order calling for widespread deployment of health information technology within ten years to realize substantial improvements in health-care safety, quality and efficiency.<sup>8,9</sup>

This period is being heralded as the "Decade of Informatics" as evidenced by national efforts to adopt key established and emerging standards in health care (CDA, HL7, CCOW, LOINC, CDISC, BRIDG and others).<sup>10</sup> These standards efforts, as well as the supporting vocabularies and ontologies (e.g. UMLS and SNOMED), need to be deeply instantiated into software development to ensure interoperability<sup>11</sup>. The CCTI and its home Department of Biomedical Informatics are leaders in these efforts and will ensure the uniform adoption of these national standards and ontologies in the CTSI and throughout the CTSA network.

**Local and National Problems to be addressed by CTSA.** Communications through educational efforts will be key to the adoption of informatics tools across the research community. Sharing of tools among CTSA funded sites will require development of an interoperability plan and will help to "de-siloize" informatics tools. This is a critical problem as there is significant redundancy of effort both within institutions and between institutions with no "ideal" environment at any institution to date. A recent report by U.S. Academic Health Centers showed that many sites "...had achieved breakthroughs in individual aspects of clinical research IT, for example, adverse event reporting systems or consent form templates. However, overall implementation of IT to support clinical research is uneven and insufficient..."<sup>12</sup> Hence it is critical for CTSA to promote the sharing of "best of breed" solutions among national CTSA sites through a robust IT infrastructure.

### **Informatics tools and resources currently available for the CTSI.**

Considerable progress has been made in developing tools to support translational research in several key areas including: clinical trials, biorepositories (tissue and serum banks), collaborative honest broker tools, data warehousing and data mining, and general tools for the support clinical and translational research design and operational management. This section provides a brief, but by no means exhaustive, overview of some of the tools developed and utilized at the University of Pittsburgh. These tools are highlighted as they exemplify the tools most relevant to the needs of the CTSI. A more complete list, in summary form, is provided in Table E. All tools listed in Table E are expected to be available to the CTSI and the national CTSA network.

CCTI's secure intranet serves as the gateway for all CCTI's applications and services. The user interface is designed to mirror the organization so that users will find navigating through the site familiar and simple. This base architecture has multiple security features including application-level, database-level, and web server access control and firewalls. It supports single login and provides a user profile management interface. CCTI is home to the Java application servers and serves applications via HTML and Cold Fusion pages. The secure CCTI intranet has been in production since 1999 and has state of the art data security systems and monitoring. These features provide a scalable environment that will provide a smooth transition for CCTI to support CTSI.

### Clinical Trials Support:

*The Clinical Trials Management Application (CTMA)* is a software tool that supports the entire lifecycle of a clinical trial, from IRB submission through open accruals to monitoring of treatment milestone activities for patients in the study. The overall goal of the system is to create a secure, web-based, integrated application to support the various clinical and administrative functions of the clinical trials process. CTMA provides functionality in the following areas: 1) administrative and regulatory management, 2) clinical research data management, 3) study parameter (adverse event, protocol event tracking, etc.) management and 4) flexible reporting for research reports. These functions have a wide range of features such as patient screening/registration tracking; IRB approval, submission, and renewal tracking; patient treatment scheduling; adverse event documenting; integrated in-house scheduling with a calendar/schedule viewer (showing scheduled appointment information for the protocol); electronic case report forms to allow users to create forms specific to their protocol; listing of protocol-associated disease registry services; and clinical data collections for fiscal-based reporting. CTMA can electronically capture and manage a variety of clinical data such as clinical responses, drug administration, extent of disease, and trial-related chemical and hematological lab results. Other clinical data which can be collected and used for research analysis, include specialized therapeutic regimens, pathology/ laboratory results, vaccination administration, and disease biomarkers. Further, CTMA allows financial monitoring of fee-based transactions such as those for special or standard testing. Thus, during the course of a trial, financial activity can be monitored and tied to the treatment regimen for each patient. With the flexible design of the CTMA system, virtually any research data generated from a clinical trial can be collected, managed, stored and viewed for analysis by the investigator, statistician, or any person(s) needing clinical-based research data.

CTMA has been widely deployed at the Academic Health Center. Developed initially for the University of Pittsburgh Cancer Institute (UPCI), where it has been live since March 2000 and is already utilized for all clinical trials, the CTMA currently supports over 500 clinical trials at the University of Pittsburgh. The Office of Clinical Research, Health Sciences (OCR), under the direction of Dr. Reis, has worked closely with the CCTI team to successfully implement it for a wide variety of non-cancer clinical trials in the Graduate School of Public Health, School of Medicine (cardiology and psychiatry), School of Nursing, and the School of Pharmacy. With CTMA, the OCR can potentially manage every aspect of clinical trials research at the University of Pittsburgh and UPMC (see letter of support from Dennis Swanson, Director UPMC Clinical Trials office). Primary data capture, storage, archiving and preparation for statistical analysis for all clinical trials is managed by CTMA. CTMA directly ports data elements relevant to clinical trials to a central Oracle data warehouse. The majority of the systems in CCTI are architected on the same Oracle database and will utilize the same data warehouse and data management schema. All are secure, structured and intranet accessible to investigators (handled by both the CTMA and data warehouse administrative modules).

*CTMA and BRIDG*: New national initiatives such as the cancer Biomedical Informatics Grid, caBIG<sup>TM,3</sup>, led by the National Cancer Institute's Center for Bioinformatics, are driving future efforts related to and versions of CTMA to exploit tools being developed in the areas of biorepositories, bioinformatics, imaging and population sciences. CCTI is a major funded development center for caBIG and is one of several organizations leading a national clinical trials modeling effort, known as the Biomedical Research Integrated Domain Group (BRIDG) model<sup>13</sup>. This is a comprehensive domain analysis model representing trials-based clinical and translational research. It was developed to provide an overarching model that could readily be comprehended by domain experts and would provide the basis for harmonization among standards within the clinical research domain and between biomedical/clinical research and healthcare. CTMA data models are currently being mapped to coincide with national standards including the common data elements, standardized vocabularies, and domain objects provided by BRIDG. This will allow CTMA to share valuable data nationwide via Grid technologies, providing a more standardized (and scalable) way to fulfill the NIH requirement for data sharing.

#### Clinical Annotation of Biospecimens and Management of Biorepositories:

Dr. Becich's group is a national leader in the development of software and strategies to support biorepositories (serum and tissue banks)<sup>14</sup>. Currently, the CCTI team manages tissue banking software supporting a national prostate cancer resource (Cooperative Prostate Cancer Tissue Resource or CPCTR<sup>15-18</sup>) and a state wide biorepository/ biomarker effort (the Pennsylvania Cancer Alliance Bioinformatics Consortium or PCABC<sup>19,20</sup>) and is a lead developer in the national effort to integrate and share data collected by tissue banks from the Cancer Centers program of the NCI (caBIG<sup>3, 21,22</sup>). The tissue banking informatics efforts of CCTI are currently supplying open source software to 18 cancer centers and research institutes across the U.S..<sup>14-21</sup>

Critical to the success of biorepositories is the clinical annotation of tissue and serum specimens. The annotation of these biospecimens with clinical data -- disease staging, severity, progression, treatment and outcomes measures --heightens their value in translational research, particularly, in biomarker discovery. Unfortunately, most of this data is not machine readable and is buried in text based reports. As part of the Shared Pathology Informatics Network<sup>22-26</sup> the CCTI has developed significant expertise in natural language processing<sup>24</sup>, de-identifying<sup>23</sup>, autocoding<sup>25</sup>, and structuring the representation of data<sup>26</sup> for use in data warehouses. The open source software for this effort, Text Information Extraction System (SPINTies), has been made available to the research community<sup>27</sup> and is the basis of ongoing development in the caBIG program as caTIES (Cancer Text Information Extraction System)<sup>28</sup>. caTIES was initially released in July 2005 to deal with information extraction from free text and tissue accession. It is a general purpose text information extraction tool to automate the process of converting free text surgical pathology reports into structured data and of storing those data in a federated capacity to facilitate retrieval, advanced query, and further analysis of pathology information. Additionally, caTIES structures data based on ISO 11179 compliant Common Data Elements (CDE), which will be accessed from NCI's cancer Data Standards Repository (caDSR)<sup>29-31</sup>. This system has already made available over 400,000 patient cases for use in University of Pittsburgh research efforts and has features that allow users to query large archives of paraffin blocks via surgical pathology reports, to request a study cohort (through an honest broker module), and to fulfill a research request from an authorized user. This system is in place at University of Pennsylvania, Thomas Jefferson University, and Washington University as well as in CCTI.

The caTIES engine and user interface are based on the General Architecture of Text Extraction (GATE) software<sup>32</sup>. GATE is a Java-based, open source framework for language engineering developed by the University of Sheffield, England. In addition, it uses the Open Grid Services Architecture Data Access and Integration (OGSA-DAI) system to enable federated services. caTIES is being adapted to work with other forms of text based records (e.g. H&P, consult letters and others).

In addition to caTIES, the CCTI team is also involved in developing a system for broader clinical annotation of biorepositories that will interface with anatomic and clinical pathology lab systems, disease registries, and radiology systems. This system called caTISSUE Clinical Annotation Engine (or caTISSUE CAE)<sup>28</sup> allows for automated longitudinal annotation of biospecimens through structured data entry that is based on national standards and vocabularies. Importantly, caTISSUE CAE provides for both manual data annotation and the import of legacy data through an applications programming interface or API. Together with caTIES, caTISSUE CAE provides a complete set of tools for managing hundreds of thousands to millions of paraffin blocks along with tens of thousands of fresh, frozen tissue and serum samples collected during routine clinical care or clinical trials. These systems provide the ability to manage retrospective archives of pathology specimens (caTIES) as well as prospectively collected tissue and serum (caTISSUE CAE) into one integrated data warehouse. Finally, through the use of de-identification tools<sup>23</sup> (delivered in a service oriented architecture) and an honest broker module, researchers can query biorepositories to identify cohorts for study, generate a “shopping cart” like request and have the “order” fulfilled after appropriate IRB documentation is provided. Most importantly, these systems provide researchers with the ability to query, browse, and acquire annotated tissue data and biospecimens across a network of federated sources. This could potentially allow for linking CTSA biorepositories across the country, making them available to an unprecedented number of researchers.

#### Collaborative Honest Broker Service:

The CCTI team developed the first, cross-departmental, collaborative broker service which has now been modeled by dozens of sites nationally. Approval for this service was received on May 8, 2003 (IRB Approval # HBO15). There are currently 28 honest brokers included in this service: 12 from the Health Sciences Tissue Bank, seven from clinical outcomes, and nine from disease registries. All honest brokers involved with this service are certified in accordance with IRB policy. HBO15 is now the “gold-standard” model used by the UPMC’s Clinical Trials Office and the University of Pittsburgh’s IRB.

The mission of this Honest Broker Service is to ensure compliance with guidelines of regulatory agencies including the Office of Human Research Protection of the Department of Health and Human Services, the Health Insurance Portability and Accountability Act (HIPAA), and the University of Pittsburgh Institutional Review Board (IRB). This facilitates the regulated utilization of protected health information, involving data stored in applications developed, managed, and/or utilized by CCTI with the following objectives:

- Enhance collaborative research efforts in CTSI;
- Monitor requests for information and data use practices via a web-based tracking tool;
- Assure IRB documents contains required identification of the broker service and specific broker(s);
- Centralize training and management of honest brokers;

All data requests are tracked in a secure, web-based data request tool, regardless of whether the purpose is clinical or research-related. Not only does this tool provide the capability of trending use of Registry and other data sources, but it also serves as a mechanism for assuring compliance with IRB policies through tracking of broker certification and IRB-approved/exempt projects. Standard reports are available within the tool. To date over 1,000 requests have been fulfilled using the CCTI Collaborative Honest Broker services, which have significantly streamlined the process for members of Health Sciences research community.

#### Clinical Research Information Services (CRIS) and De-Identification (De-ID) Software:

CRIS is a jointly sponsored service of the Office of Clinical Research, Health Sciences (OCR) and the CCTI. CRIS is available for use by faculty in the Schools of the Health Sciences and for UPMC special projects requiring de-identified datasets. CRIS is a certified honest broker with the University of Pittsburgh IRB and has a business associate agreement with UPMC. The policies and procedures of CRIS are posted on the OCR website.<sup>33</sup> CRIS uses the De-ID application developed by the Center for Biomedical Informatics at the University of Pittsburgh and licensed by the University to De-ID Data Corp, Philadelphia, PA. The De-ID application is used by the NCI and other academic medical centers for various research applications.

De-ID uses a set of heuristics to identify the presence of any of the 17 specific HIPAA identifiers within electronically stored medical text. The De-ID application has a configurable option for either Safe-Harbor or Limited Data Sets. De-ID locates identifiers in the text by firing a set of rules one sentence at a time. For any of the potential identifiers removed from the text, a corresponding tag is left to hold its place. For example, when a telephone number is removed from text, the tag “\*\*PHONE-NUMBER” is left in its place so that the reader can see the type of information that was removed. Names found multiple times in the report are consistently replaced with the same tag to improve readability. Supplemental dictionaries of geographic locations, hospital names, and popular names found in the U.S. Census are used to locate identifiable text, and the UMLS Metathesaurus is utilized to ensure that medical terms or phrases are preserved.

De-ID automatically creates a linkage file when a dataset is processed. The linkage file is stored in an encrypted format and is only available for viewing by an honest broker who has the necessary password key. The study identifier is a two-part code; part one is the number of the report for that patient; and part two is a unique 12 alphanumeric code for that patient. This is structured so that the study ID remains consistent across data sets while different admissions and/or multiple reports can be easily identified. The Center for Biomedical Informatics (CBMI) performs formal evaluations of the De-ID software.<sup>23</sup> In addition, the output generated by De-ID is briefly reviewed by an honest broker prior to releasing it to the investigator. Improvements to De-ID are done monthly based on lessons learned from the use of the application.

#### Data Warehousing and Medical Archival Repository (MARS):

MARS was developed at the University of Pittsburgh in 1986 to improve health care by integrating the computer systems that supported medical care at the departmental level.<sup>34-36</sup> The concept was to create a complete electronic medical record repository that would facilitate clinical and translational research. The focus of the program has now extended to all patients seen at the UPMC's 19 hospitals, physician offices, and outpatient clinics. MARS currently houses 115M clinical reports and 335M financial transactions. It is estimated that almost 500,000 new clinical reports and 450,000 financial transactions are received each week. Approximately 15,000 - 20,000 reports are retrieved daily for the support of clinical activity, and there are approximately 6000 logins each day.

All records obtained on a single patient at any given time are linked via a unique patient identifier. Patients who cross institutional (hospital) domains are linked through a Master Patient Index. In addition, a minimum of three demographic items are stored with each record. This strengthens linkages and facilitates searching for common patient characteristics within clinical and financial records. Diseases are classified using ICD-9 codes and include drug-induced diseases (E-codes). These codes are available in each patient's medical record discharge abstract. Drugs and biologics dispensed through the pharmacy are coded individually as well as by class using the American Hospital Formulary Service system. Pharmacy data such as drug, dose, start/stop dates are available on MARS from 1990, as well as real-time orders, allowing for clinical reminders and alerts to be used at the time of drug ordering. Complex multiple drug profiles can be reconstructed and temporally related to clinical events.

Each record in MARS is a collection of stanzas defined by a database dictionary. For clinical records, there are demographic stanzas containing identifiers, such as name or patient identifier; classification stanzas which define record types and dates; administrative stanzas defining origins of records and dates of processing; and document stanzas containing the bodies of reports. As of 2005, there were over 12 billion search tokens available from clinical documents and over 500 million demographic items indexed. Any word or combination of words in any stanza or combination of stanzas can be used to locate any part of any record through a general Boolean query language which supports AND, OR, and NOT with the use of distance operators. Because every word of every record contained in MARS is indexed, precise search patterns can be formulated and cross-correlation is enhanced.

Each record in MARS database is assigned five security tokens. The tokens are defined by hospital domain and by content area (e.g. psychiatric, juvenile and other sensitive areas). Each user can be authorized to access medical records by domain and by type. Every search and every record access is logged to a daily security file. A summary of each search is sent to the user's supervisor via email each day. Security logs are maintained for two years on-line and indefinitely on backup.

In summary, MARS is a central research tool supporting the clinical and translational research of CTSI. An important aspect of its use is for identifying patients for participation in clinical trials.<sup>35</sup> Hundreds of clinical trials and research projects are currently using MARS and all departments at Pitt/UPMC rely on it daily for their translational research needs.

#### GCRC Information Technology Core:

The Information Technology Core (ITC) of the GCRC evolved from the integration of a long standing biostatistical core of the GCRC (over 10 years) into an Information Technology Core created within the Center for Clinical Pharmacology by Dr. Branch and merged into GCRC support in 1999. The ITC has been an effective infrastructure support to the entire GCRC clinical research operation at the four clinical sites. Each component has provided statistical and informatics review of each protocol approved by the Scientific Review Committee before a protocol receives approval for support. In addition, the informatics component has provided three major services. The first has been to assist the administrative function of the GCRC by creating and managing an integrated internet and intranet portal that not only provides information about the research center, but also offers a dynamic exchange of information used in protocol management and patient scheduling. The ITC has developed and manages an all electronic web-based protocol review mechanism, has

established a Protocol Data Management System (PDMS), which is managed by the GCRC administration and routinely used by nursing staff, nursing coordinators and investigators. This system is linked to a patient scheduling system that manages space and staff utilization on a protocol by protocol basis. This system is also offered as a management tool for a bar coding laboratory tracking system for biological samples. These innovations and their incorporation into standard working practice have increased GCRC efficiency by approximately 40% in the last three years.

In addition to conventional features such as electronic form development, relational base advice, and security and back up services, the ITC has specialized in using on-line analytical processing (OLAP) technology on top of an Oracle relational database. This is of particular value to translational research, which acquires multiple domains of complex information. The ITC has also acquired expertise in providing valuable service in clinical research team communications by promoting team building tools such as Bridgit™, SharePoint™ and telecommunications. Provision of this service as a front end introduction to clinical investigators of the value of IT has led to the education of young investigators and requests from investigators to assist in more complex IT management. Each of the three services -- administrative support, investigator assistance and education -- will be maintained and offered to a broader array of investigators through its incorporation into the CCTI.

#### Online Research Communities:

The concept of a CTSI Online Research Community (ORC) builds directly on a recent grant for a global Dental Informatics Online Community (DIOC) awarded to the Center for Dental Informatics by the National Library of Medicine (GO8-LMO8667; 4/1/06-3/31/09). This project, developed by the Universities of Pittsburgh, Michigan, Harvard, and Uppsala in Sweden, will establish a networking platform for individuals interested in dental informatics research in order to promote the development of dental IT and informatics research, to disseminate results, and to encourage the formation of research and education partnerships. DIOC compiles detailed requirements based on an assessment of information needs of informaticists, researchers, educators, and clinicians. It uses open-source tools and a state-of-the-art, user-centered software development process and evaluates the impact on informatics researchers using archival and survey data. DIOC's innovation is based on previous work by the Center for Dental Informatics team.<sup>37,38</sup>

In a second, related effort, computer-based collaborative tools in the NYU Oral Cancer Research for Adolescent and Adult Health Promotion (RAAHP) Center, funded by the National Institute for Dental and Craniofacial Research (1U54DE14257-01; 8/1/01-7/31/07)<sup>39</sup> have been implemented and evaluated by CCTI members. In the RAAHP Center, 10 widely geographically distributed institutions are collaborating to reduce oral health disparities in oral cancer. CCTI is supporting the scientific activity in the Center using off-the-shelf collaborative tools. To establish the electronic collaborative infrastructure, semi-structured interviews, surveys, and contextual inquiry were used to assess user needs and define technology requirements. Commercial software applications were then evaluated and selected by comparing their feature sets with requirements followed by pilot-testing of selected applications. Local and remote support staff cooperated in the implementation and end user training for the collaborative tools. Collaborating staff evaluated each implementation by analyzing utilization data, administering user surveys, and functioning as participant observers. Tool adoption and use was successful in groups whose task and interaction requirements closely matched the feature set of the tools. Support and adaptation of online collaborative methods will be critical to CTSI's effort to communicate and share research tools and results with the CTSA community locally and nationally. An Online Research Community (ORC) will facilitate these efforts as described in Specific Aim 3.

## **CORE DESIGN and METHODS**

### **Overview of translational and clinical research facilitation and integration through the CCTI:**

The CCTI will enhance clinical and translational research, instruction, and dissemination, and it will foster innovation within CTSI and with all collaborating CTSA sites. The approach to achieve this goal includes a mechanism for promoting both internal, intra-institution, and external interoperability software, which will allow for communication among CTSA sites and with the research partners of clinical and translational investigators (e.g., government, clinical research networks, pharmaceutical companies, commercial vendors, laboratories, and equipment manufacturers). CTSI's translational informatics plan relies on secure, workflow-driven, user friendly software that is built upon national standards. The faculty in the CCTI are national leaders in the transfer of research findings into routine care, the implementation of standards in support of clinical and translational research, and the development of de-identification software, vocabulary/ontology services, and HIPAA compliant and secure systems. The CCTI team has been innovative in the development of new tools, methods, and algorithms to support clinical research.

The goal of the CCTIS is to transform processes, information management, and data integration at each step in the "lifecycle" of clinical and translational research projects. This will be accomplished by developing "open



source” tools to share with CTSA sites nationally which can be connected by grid computing to serve the research, innovation, and educational needs of the network. The following specific aims are proposed in order to implement and maintain the most advanced, available software in support of each step in the lifecycle of clinical and translational research projects sponsored by the University of Pittsburgh CTSI. The research project lifecycle spans conception and formulation, study design and planning, resource allocation, execution, intermediate and final dissemination of data, data analysis, results reporting, and long range developmental planning. This approach will enhance the efficiency of each project, research group, and the University of Pittsburgh research enterprise as a whole. It will specifically address unmet needs, particularly the seamless integration of clinical and research data and will lower or eliminate barriers to data flow in translational research from bench to bedside and from bedside to clinical practice.

**Specific Aim 1: Provide a rich set of biomedical informatics resources and integrate these under a common management team that is responsible for their implementation, customization, further development, and maintenance.** These resources have primarily been developed in the Center for Biomedical Informatics, Center for Pathology Informatics, the Benedum Oncology Informatics Center, the GCRC Information Technology Core, and the School of Dental Medicine and have been built on a variety of grants from the NCRR, NCI, NHLBI, NICDR, NSF and NLM. These already existing resources provide best-of-breed clinical and translational research tools as an infrastructure for the CTSI. They will be supported as core resources within the CTSI and as such will provide an advanced IT and biomedical informatics tool kit to support the educational mission of CTSI. CCTI will be the CTSI home for developing collaborative IT infrastructure, modeling strategies, analytical/data mining techniques, and other innovation.

#### Integrating tools to support clinical trials and clinical research:

The Benedum Oncology Informatics Center has developed a cutting edge application called the Clinical Trials Management Application (CTMA) which was recently chosen by the National Cancer Institute (NCI) as a primary tool for the support of clinical trials for the Cancer Biomedical Informatics Grid Initiative (caBIG). CTMA is a complete suite of tools to help translational researchers manage the regulatory and compliance processing associated with proposing/opening a trial, administering that trial once implemented, collecting research data for patients involved in the trial and recording adverse events on patients during clinical trials. It also acts as a tool for the eventual analysis of the research data in collaboration with biostatisticians. CTMA was designed not only for independent investigator initiated clinical trials for federally funded agencies, but also for trials contracted with major pharmaceuticals companies. This system has recently been adopted by the UPMC Health System as the primary tool for implementing, conducting, reporting, and analyzing clinical trials and for financial billing and tracking of contractual relationships with funding entities (see letter of support from Dennis Swanson, Director, UMPC Clinical Trials Office).

The CCTI team will work closely with the CTSI Research Registry (see Novel Clinical and Translational Methodologies section) to utilize BRIDG’s consent model (described above) to create the necessary interoperability between CTMA and other systems currently supporting clinical trials with the goal of creating solutions for identifying patients for clinical trials. The caBIG effort will give the CTSI Patient Registry and CTMA a high degree of interoperability and compatibility with all other caBIG-developed systems and national standards. In addition, CTMA is interoperable with clinical and financial systems to allow the management of trials and integration of clinical data from a number of enterprise health care systems. This includes but is not limited to, pathology (Cerner’s coPATH-Plus) and laboratory data (Misys’s FlexiLab), disease (outcome) registries (IMPAC’s MRS Registry), and other outcome databases that support clinical and translational studies. The major method of data transport to and from CTMA is Health Level Seven (HL7). CTMA also accepts feeds from the EPIC scheduling system and the CCTI-developed Enterprise Master Person Index. Structured data entry in CTMA is accomplished through various standardized code sets: Common Toxicity Criteria v3 (CTCv3), ICD9, SNOMED, Social Security Death index, CPT Billing codes, MedDRA, and reporting criteria from American Joint Committee on Cancer (AJCC).

A complete suite of tools to support clinical and translational research includes MARS, CRIS, Honest Broker Tools, and De-Identification software (each described above) as well as many others (see Table E). These tools, in coordination with CTMA, provide support for subject identification and recruitment (MARS and CRIS), honest broker services, de-identification services (CRIS and De-ID), and data warehouse (CRIS and MARS) and data mining support (CRIS).

CTMA is currently deployed throughout the four academic hospitals at the University of Pittsburgh. As part of the CTSI plan, CTMA will be implemented throughout the Schools of the Health Sciences and shared with collaborators regionally, if requested by the National CTSA Informatics Steering Committee. The CCTI group uses G-Forge for sharing software as described in the Data and Software section. The research plan for CTMA and the rich tools that CCTI supports includes (see Proposed Timeline for Implementation section):

1. Rollout of these applications to the entire CTSI community in support of clinical trials and studies
2. Implementation of a campus wide training, support, and maintenance plan
3. Analysis of needs and subsequent enhancement of existing tools to address user requirements across CTSI
4. Versioning all software to CTSA compliance as “open source” and grid enabled (see specific aim 2)
5. Making all software tools available through G-Forge for implementation at other CTSA sites

#### Integrating Software for Managing the Collection/Disbursement of Clinically Annotated Biospecimens:

The University of Pittsburgh has been a leader in the development of tissue banking informatics tools as evidenced by three NCI PO1's and one NHLBI contract currently utilizing CCTI tools developed for the purposes of supporting clinical trials and biomarker discovery. The University of Pittsburgh is the central site in the development of tissue banking and pathology tools for the Cancer Biomedical Informatics Grid initiative (NCI contract). Applications include a tool that manages biospecimen repositories (tissue bank inventory or TBIInv) and tools for the automated extraction of pathology data for the annotation of biospecimens (caTIES and caTISSUE CAE, each described above). These tools help to tie rich clinical annotation from clinical systems (pathology and laboratory data, outcomes registries, disease progression data, and treatment data) with the associated tissue specimens irrespective of their physical state (serum, frozen tissue, paraffin embedded tissue, RNA, DNA, or extracted protein, etc.). These tools are very important for the conduct of clinical trials and biomarker-based discovery science and; more importantly, they are critical in the validation of bench to bedside translational research. These tools also manage data affiliated with tissue microarrays, which are high throughput methodologies for validation studies critical to disease based research.

This entire suite of tools which was developed in the pathology and oncology programs at the University of Pittsburgh will be scaled into the CTSI. All of the tissue banking and pathology tools, as well as the tissue microarray tools, are open source and ready to be shared with the national CTSA community. The research plan for biorepository tools is similar to that for CTMA and includes (see Proposed Timeline for Implementation section):

1. Rollout of these tools to the entire CTSI community in support of biospecimen based research
2. Integration with CTMA to provide “transparency” to the users
3. Implementation of a campus-wide training, support, and maintenance plan
4. Analysis of needs and subsequent enhancement of tools to address user requirements across the CTSI
5. Versioning of all software to CTSA compliance as “open source” and grid enabled (see specific aim 2)
6. Making all software tools available through G-Forge (see Data and Software Sharing Section) for implementation at other CTSA sites

#### Integrating the Information Technology Core (ITC) of the GCRC into CCTI:

The ITC of the GCRC will continue to serve the Intensive Clinical Translational Research Center (ICTRC), the prior parent GCRC, as well as become an integrated component of the CCTI. In supporting the ICTRC, it will maintain its vital administrative support to the ICTRC portal, web-based protocol review system, the day to day functional Protocol Data Management System (PDMS), and the operational scheduling system, which is already integrated with the CTMA Patient Scheduling tools. The support ITC provides to clinical and translational investigators will be maintained and strengthened through integration with CCTI and the rollout of CTMA. ITC's focus on creating useful tools for translational clinical research will complement and be broadened by continued enhancement of CTMA.

The existing ITC is of great value to young investigator as it provides proactive assistance in cross research team communication. This assistance will continue in the CCTI, as it increases the efficiency of research teams by providing education in the use of IT tools to assist conceptual and logistic protocol development.

#### **Specific Aim 2 Integrate Open Source Tools of CCTI Through caBIG Grid Architecture and**

**Vocabulary and Ontology Services:** “Open source” tools developed by the University of Pittsburgh's CTSI will be linked using grid computing tools developed by the Cancer Biomedical Informatics Grid (caBIG) program of the NCI<sup>29-31</sup>. This will allow all CTSI software development to migrate to an open source environment though the infrastructure provided by CCTI. The software tools described in Specific Aim 1 will then be made integrated and interoperable by the grid computing architecture, vocabulary services and syntactic/semantic networking tools provided by caBIG.

Several components of the caBIG infrastructure will need to be implemented and maintained for the CTSI. These include the following applications: *(NOTE: The descriptions here are from the caBIG website adapted for use in CCTI as agreed to by the caBIG program director, Ken Buetow, PhD – see letter of support).*

Bioinformatics Infrastructure Objects (caBIO) – CCTI will create UML models of biomedical objects to facilitate communication and integration of information from various initiatives supported by the CTSI. Model

re-use will be supported via distribution of Rational Rose representations of object models. These caBIO will then be implemented using Java 2 Enterprise Edition. The caBIO Java package can be used locally to retrieve data from CCTI servers using Java-RMI. Alternatively, caBIO data can be accessed using SOAP-XML or simple HTTP applications programming interfaces.

Data Standards Repository (caDSR) – CCTI will support a local instance of caDSR to standardize meta-data. Common Data Elements developed by CTMA, caTIES, caTISSUE CAE, BRIDG, and the honest broker toolkit will be centrally stored and managed by CCTI in the Data Standards Repository (caDSR). The caDSR has a web interface and a PL/SQL applications programming interface for programmatic access.

Enterprise Vocabulary Services (EVS) - At the foundation of a standardized approach to interoperable systems is a controlled vocabulary. CCTI will meet this need through an Enterprise Vocabulary Service (EVS). Standard vocabularies will continue to be developed for a variety of settings in clinical and translational research. Tools for vocabulary development and curation will also be created and improved through collaborations with vendors. The NCI EVS is a collaborative effort of the NCI Center for Bioinformatics and the NCI Office of Communications. The NCI Thesaurus, which is a biomedical thesaurus created specifically to meet the needs of the NCI, is produced by the NCI EVS project. The NCI Thesaurus is provided under an open content license. The NCI EVS Project also produces the NCI Metathesaurus, which is based on NLM's Unified Medical Language System Metathesaurus, supplemented with additional cancer-centric vocabulary. In addition, the EVS Project provides NCI with licenses for MedDRA, SNOMED, ICD-O-3, and other proprietary vocabularies. A major part of the CCTI development will be to expand this vocabulary in association with the UPMC Interoperability effort on the part of the Center for Strategic Informatics (see Background).

caCORE - The infrastructure backbone of caBIO, caDSR and EVS is caCORE. It is the open-source foundation upon which to build research information management systems.<sup>31</sup> caCORE systems are developed and released using professional software development practices. All caCORE resources, including the EVS vocabulary and caDSR metadata content, are now dynamically accessible through common applications programming interfaces. This feature sets the stage for full realization of the caCORE vision: consistency, clarity, and comparability of biomedical research information. caCORE provides a suite of common resources for vocabulary and metadata and data management needs. Version 3.0 represents the culmination and fruition of the CCTI vision to achieve semantic interoperability across disparate biomedical information systems. The approach uses concepts from description logic thesauri to build up the data classes and attributes in Unified Modeling Language (UML) information models. The models are registered in a metadata registry, and then turned into model-driven data management software. The caCORE Software Development Kit gives any developer the tools needed to create systems that are consistent and interoperable with caCORE. Version 3.0 also adds the new Common Security Module, a flexible framework for application security that can fulfill refined and highly granular access control requirements. Detailed info on architecture/content can be found in the caCORE Technical Guide.<sup>40</sup>

caGrid - The caGrid 0.5 software release contains tools for creating and deploying software developed utilizing caDSR, EVS and caBIO infrastructure. caGrid 0.5 provides the infrastructure necessary for CTMA, caTIES and caTISSUE CAE to leverage the following grid infrastructure capabilities: indexing and registry services, metadata management, common data elements, controlled vocabulary semantics, xml schema management, security services, discovery and invocation, data service toolkit, and an analytical service toolkit. caGrid itself leverages the following existing technologies: 1) Globus Toolkit (Version 3.2.1): Provides the core grid infrastructure and supports service deployment, service registry, invocation, and secure communication, 2) Open Grid Services Architecture Data Access and Integration (OGSA-DAI) (5.0): Provides core support for data services, 3) caDSR, 4) EVS, and 5) Mobius GME: Grid Repository for XML Schemas. caTIES has been successfully deployed as a reference grid implementation and additional developed software will be added to the caGrid in the upcoming months.

The research plan for specific aim 2 is as follows (see Proposed Timeline for Implementation section):

1. Implement local instances of caDSR and EVS in CCTI's development environment for CTSI
2. Work with UPMC/U Pitt to establish a vocabulary and ontology service for CCTI through the Center for Strategic Informatics (UPMC sponsored, see background section above)
3. Load the UML-model-based common data elements from CTMA into caDSR and generate corresponding application programming interfaces via caCORE. Note: Already completed for caTIES and caTISSUE CAE.
4. Establish the aforementioned Grid services for CCTI and CTSI
5. Release version 1.0 of CCTI's Grid service enabled software for clinical and translational research (CTMA, caTIES, and caTISSUE CAE)

6. Continue to migrate tools developed by the caBIG program (caGEDA, caTISSUE Core, caARRAY, R-Proteomics, PIR, and others) to the CCTI Grid instance at CTSI, leading to the release 2.0 of CCTI's Grid-service-enabled software for clinical and translational research
7. Use the University of Pittsburgh CTSI Grid services as an evaluation test bed to propose a CTSA pilot of this infrastructure at additional locations determined by the NIH CSTA Informatics Steering Committee.
8. If this grid-enabled, standards-based architecture is found useful, establish the CCTI as a training and education site on the implementation and support of these tools.

**Specific Aim 3 CTSI Online Research Community:** The CTSI Online Research Community (ORC) (see Figure 1) is a rich collaborative information technology (IT) infrastructure, that, combined with systematic training in informatics and information technology, will significantly increase the effectiveness and efficiency of research within the CTSI. The ORC includes four major components: Directories of People, Projects, Resources, Tools and Events; the Learning Center; Intelligent Information Routing Through Infrastructure; and a Basic Customer Relationship Management System. These components will be implemented and evaluated through: Needs Assessment and System Architecture; Implementation; and Evaluation. Development of the ORC is strongly supported by both the School of Dental Medicine (see letters of support from Drs. Braun and Weyant), and the overall IT support organizations Health Sciences-specific and University-wide support units (see letters of support from Jim Adamczyk and Jinx Walton, respectively).

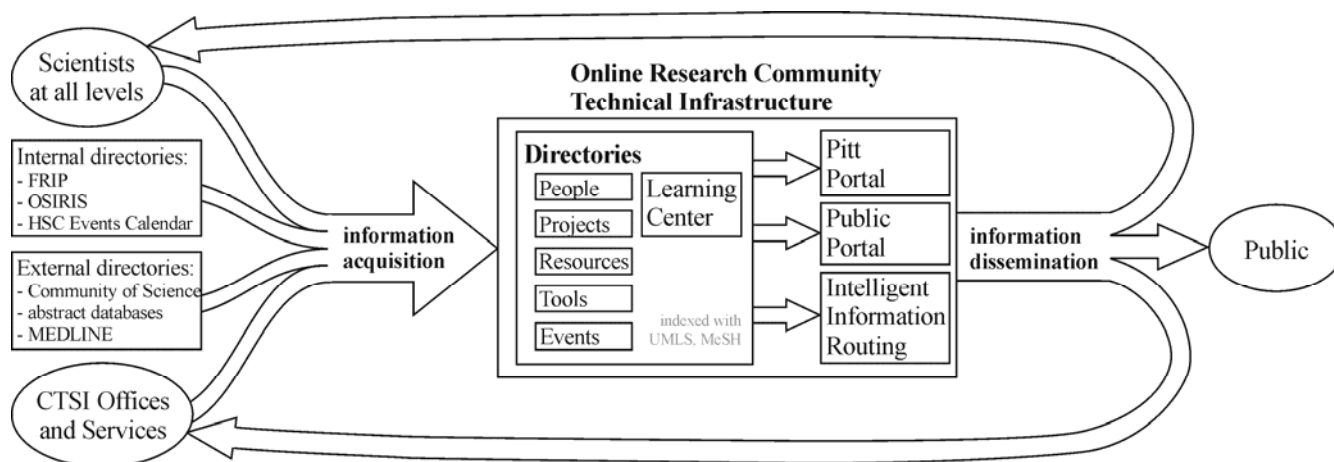


Figure 1: Overview of the CTSI Online Research Community (ORC)

**Directories of People, Projects, Resources, Tools, and Events:** A key component of the ORC will be directories of people, projects, resources, tools and events. Several of these directories will build on existing projects in place at the HSC, such as the Faculty Research Interests Project (FRIP) and the Online Submission for Institutional Reviews (OSIRIS) system. The records in those directories will be based on standardized templates and described using terms from a controlled vocabulary (the Unified Medical Language System with local extensions). The people directory will include all individuals involved in research, regardless of their role. For scientists, a detailed personal profile will describe research interests, publications, grant support and ongoing research projects. This directory will be built on FRIP, a system that contains faculty research interests expressed through MeSh-terms.<sup>41,42</sup> The project directory will be a listing of research projects populated from a variety of sources, such as the OSIRIS system, maintained by the University of Pittsburgh's Institutional Review Board (IRB), and project descriptions provided directly by investigators. Over time, the project directory will be augmented by adding other useful artifacts and key documents produced over the course of a research project, such as instruments, abstracts, technical reports and presentations. A section on research resources and tools will provide a comprehensive directory of the computational research tools and services described in Specific Aim 1. The directory will contain a description of each tool and its purpose, a tutorial about its use, contact and development personnel, studies/projects completed using each tool, and resultant publications. In addition to domain-specific research tools, the directory will also offer documentation and implementation assistance for selected commercial, off-the-shelf collaboration tools, such as Groove and SharePoint (both from Microsoft Inc., Redmond, WA) that will be licensed and supported by the University's own Computing Services and Systems Development (CSSD) unit. The existing Health Sciences events calendar will also be incorporated into the CTSI directories. The directories will have sophisticated end-user, administrative, and machine-machine interfaces (e.g., RSS-feeds) and be searchable in a flexible and powerful manner.

**The Learning Center:** The Learning Center is a specialized on-line directory for learning and training that contains a comprehensive index of the educational resources within the CTSI. It should not be confused with

the learning management systems, such as Blackboard (Blackboard, Inc., Washington, DC), in use at many universities. It can be best thought of as a one-stop gateway that guides learners at any level, from the college student to the experienced investigator, to the learning experiences most appropriate for their goals. These learning experiences can be historic (e.g. archived Webcasts), episodic (e.g. single seminars), or programmatic (e.g. courses or programs). The Learning Center will include a variety of materials, such as tutorials, Frequently Asked Questions (FAQs), presentations, Webcasts (both real-time as well as archival), course and lecture descriptions, and educational programs (see Education section of CTSI). The Webcast archive will build on an existing program of providing Webcasts to faculty and residents<sup>43</sup> that has been in place since 2002 and currently contains over 630 archived presentations.

**Intelligent Information Routing:** Both the Directory and Learning Center components of the ORC are focused on creating highly structured, user-focused collections of information relevant to research within the CTSI. In part, those resources are intended to be accessed by users and administrators on demand through a CTSI Web portal. However, this approach, by itself, is insufficient to result in successful adoption of the ORC within the CTSI. Therefore, the ORC will implement the concept of Intelligent Information Routing through the use of an ontology. This approach recognizes that individual attention is a rapidly diminishing resource, and that the ORC can only succeed if it delivers relevant, targeted information that is intimately connected to the information needs and core activities of each member. Therefore, the ORC will include a Current Awareness Service (CAS), which automatically routes information that fits a member's profile,<sup>44</sup> such as funding opportunities, new projects, and potential collaborators. In addition, the ORC will provide individually customized information whenever a member interacts with the ORC. For instance, when a new member enters his/her research interests, the ORC will automatically list other members with similar interests and related projects. Information distributed through the ORC will be non-duplicative and highly targeted, since an excessive number of irrelevant alerts will turn off valuable members.

**A Basic Customer Relationship Management System:** The ORC will incorporate a basic Customer Relationship Management (CRM) system that will provide a tracking mechanism for interactions of scientists with the CTSI as a whole. This system will not only provide a valuable mechanism for directing the course of an individual research project through the CTSI, but also provide valuable information for the evaluation of the overall CTSI effort and outcomes. Initially, this system will catalog a scientist's interaction with the electronic resources, such as the ORC, made available by the CTSI. As a second-stage development, the CRM will be used to track interactions with offices and services within the CTSI. For instance, the CTSI Research Facilitators can use the CRM to make sure that an investigator is working with all relevant resources and people in pursuit of a specific project. Investigators will be able to "opt out" of this voluntary tracking methodology.

**ORC implementation and evaluation:** The ORC will be implemented and evaluated through three activities, which will initially follow each other in sequence, but will be repeated multiple times during the project period. The activities are Needs Assessment and System Architecture; and Implementation and Evaluation. In the Needs Assessment and System Architecture activity, the needs and requirements of the CTSI community will be determined.<sup>45</sup> The ORC's target groups will range from undergraduate students to senior researchers, and the needs assessment will be correspondingly broad. Assessment will employ focus groups, surveys, and contextual inquiry<sup>46</sup> of researchers; research-active departments; the School of the Health Sciences; school-, HSC-, and university-level research administrators; and entities such as the Office of Research, the IRB, and the Office of Academic Career Development. The system architecture will be defined in collaboration with existing IT support entities at the University of Pittsburgh, and build closely on existing computational resources and services. For Implementation, existing on-campus and external community building tools (e.g., open source tools, such as G-Forge, and commercial applications, such as SharePoint) will first be researched and evaluated in terms of their suitability for implementing the ORC. The ORC will be implemented through existing computing resources maintained by Health Sciences-specific and University-wide support units (see letters of support from Jim Adameczyk and Jinx Walton, respectively). Evaluation will comprise both ongoing formative evaluation during the development process of the different ORC components as well as summative evaluation of the online community as a whole. Formative evaluation will involve methods such as structured group feedback on plans and designs for the ORC, interviews, focus groups, surveys, expert reviews, paper prototyping, and usability testing. Summative evaluation will employ focus groups, surveys, and bibliometric and utilization analyses. Evaluation measures will include usefulness and ease-of-use as perceived by end users, community participation rate and patterns, contribution to and access of directory information, co-authorship and collaboration patterns for research projects, and other CTSI outcome measures.

**ORC Summary:** The ORC can provide significant value to the CTSI effort, but only if it is adopted by most participants in research at the University of Pittsburgh. Therefore, "designing for adoption" is a major guiding

philosophy. First, the ORC will be designed with the researcher as its central user. User-centered design methodologies,<sup>47</sup> which have been used successfully in other projects, will ensure that the ORC meets the information needs and functional requirements of its members as much as possible. Second, the ORC will take advantage of existing information repositories, such as the FRIP, the OSIRIS and the Health Sciences Events Calendar, in order to eliminate any duplication of data entry. In a later stage of the project, external entities to which researchers contribute data, such as the Community of Science and major conferences, will be tapped with the expectation that their databases will be a source of material for the ORC. As a consequence, the ORC will, as much as possible, minimize the data entry burden for the individual investigator. Third, intelligent information routing will significantly reduce the effort to extract useful information from the ORC for each community member, will eliminate a large barrier to participation, and will address the critical mass problem in online communities.<sup>48</sup> Lastly, participation in the ORC will be voluntary. Although scientists may not want certain information about their research made public, it is expected that most scientists will engage in and contribute to the ORC due to the considerable benefits that the system possesses.

The ORC will have a rich public “face” within the University of Pittsburgh, and a more limited one for the world at large. This approach acknowledges that scientists must, in order to remain competitive, protect their ideas and projects from public access to a certain extent; however, they also depend on exposing their ideas in order to gain qualified collaborators and advance their project. The ORC will therefore keep selected information in its directories confidential, but also implement a public version of intelligent information routing.

While the ORC has its roots in research at the University of Pittsburgh, over the long term, it is a resource that will serve many other communities. For instance, the close collaboration of the University with other local research organizations, such as Carnegie Mellon University, requires that the ORC have a rich external interface and permeable information boundaries. Thus, investigators outside of the University may participate, and in turn enhance the University’s research efforts. Second, ORC tools will be made available to other CTSI awardees in the true spirit of open source software development. In summary, ORC is an integral part of CTSI’s communications and training. It is key for the dissemination and training of investigators on the informatics tools in CCTI. ORC will be used by cores, project managers, research liaisons, and community partners to develop novel ideas and accomplish the goals of the CTSI.

An example of how the ORC might facilitate the development of novel ideas is provided in the CCTI’s plan to develop and support data mining tools, which will be made available to CTSI investigators via the ORC. Data mining involves analyzing data for relationships that have not previously been discovered. As clinical and translational research generate increasing amounts of data, including high throughput genomic and proteomic data, the opportunities to discover unknown relationships of clinical importance increase significantly.<sup>49</sup> Data mining often is characterized by computationally intensive algorithms that are applied to databases with large numbers of variables, records or both. The methods are similar in spirit to exploratory data analyses within statistics. Indeed, a number of data mining methods, such as neural networks, and memory-based algorithms, have become part of popular commercial statistics packages, such as the SAS Enterprise Miner. However, there are many useful data mining methods that remain unknown to most clinical and translational researchers. ORC content will be developed to facilitate clinical and translational researchers learning about and applying data mining methods to their research data. Three examples are illustrated here. A number of the computer methods available<sup>50</sup> are applicable to exploring relationships between single or multiple SNPs and patient phenotypes<sup>51</sup>. CTSI researchers need help in locating the most applicable methods and learning how to use them appropriately. As a second example, methods for learning probabilistic networks have proven useful in inferring biological pathways from high throughput data.<sup>52-54</sup> A number of such methods are available on the web,<sup>55</sup> but users unfamiliar with these techniques need help in choosing and applying them appropriately. As a third example, rule-learning methods have yielded models that accurately predict patient disease susceptibility using mass spectrometry measurements of patient proteins.<sup>56</sup>

In keeping with the overall design of the ORC project, data mining methods that are most likely to be useful to CTSI researchers will be cataloged, organized, and documented, and web links to these methods will be provided. A directory of people and projects at the University of Pittsburgh who have used particular data mining tools in their research will be provided. Online tutorials about data mining methods, complete with clinical examples of their application, will also be developed. Intelligent information routing will send researchers suggestions regarding applicable data mining tools, based on those researchers declared interests. As new methods are developed and cataloged in the ORC, new information will be pushed to the researchers for whom those methods are most relevant.

**Integrating Training in Biomedical Informatics into the K-12 program:** The section on Research Education, Training and Career Development describes three coordinated doctoral training programs in clinical and translational science (CTS). These programs train individuals in the skills required for translating

scientific and technological advances into clinical practice. One program provides a concentration in biomedical informatics (BMI). In that program, all trainees receive a fundamental grounding in CTS through coursework, immersion in CTS-rich environments, and mentoring. In addition, the trainees learn how to apply biomedical informatics methods and concepts to CTS research problems through BMI coursework and research opportunities. As one example of a research project, a trainee might investigate methods and models for providing effective alerts to clinicians, based on information in an electronic medical record that describes key aspects of a patient's genome, proteome, clinical state, and current medications.

Trainees in the program will typically enter with an advanced clinical degree, such as an MD. Funding will be provided through several mechanisms at the University, including CTS training funds, the K12 multidisciplinary training grant (for trainees with multidisciplinary translational interests that includes biomedical informatics), and a biomedical informatics training grant from the National Library of Medicine. Upon obtaining an advanced degree, these individuals will be prepared to carry out independent research in biomedical informatics as applied to CTS problems. Most graduates will likely obtain positions in academia, but some will work in the private sector to commercialize advanced informatics systems to support CTS.

A doctorate in CTS/BMI will be offered by the BMI training program within the School of Medicine; this program has offered M.S. and Ph.D. degrees in BMI since 2001. The CTS/BMI training program faculty currently consists of nine core faculty in the existing BMI training program and faculty in the Clinical Research Training Program (CRTP). These faculty members already have a history of close cooperation in developing joint programs (e.g., an existing M.S. concentration in Health Services Research within the BMI training program), in jointly teaching courses, and in co-mentoring students. The BMI and CRTP training programs are collocated in adjoining floors of the same building, which is in close proximity to the University of Pittsburgh Health Center, to the Schools of the Health Sciences and to the main University of Pittsburgh campus.

**Administrative Structure of CCTI:** Dr. Becich will direct the CCTI, be a member of the CTSI Steering Committee, and participate in the Internal and External Advisory Board. He will establish a CTSI Informatics Working Group to monitor the activities of CCTI with weekly operations meetings organized by the project manager. He will participate in the National CTSA Informatics Steering Committee that will establish standards, best practices, and/or determine adoption of Informatics tools. CCTI is clearly committed to working to ensure interoperability for its clinical and translational investigators and is a national leader in these efforts. The CCTI team has established a strong track record as a leader in data and software sharing. All publications will be submitted to the NIH manuscript submission (NIHMS) system at PubMed Central (PMC).

**Evaluation Plan for the CCTI:** Assessing the progress of the CCTI towards transforming information management and data integration in clinical and translational research will require applying a suite of evaluation methods over the entire lifecycle of the project. This effort will be led by Valerie Monaco, MHCI, PhD who is an expert in evaluative methods and trained in Psychology and Human Computer Interaction. The methods to be employed include formative and summative approaches to evaluation and will address the questions: "What is the current workflow for researchers and how can we best build and adapt our applications to support and enhance their workflow?", "What are the important performance metrics associated with this application (e.g., accuracy, speed, etc) and how well is it functioning?", "How do researchers interact with our tools and how can we improve the usability of the tools?", "How are researchers utilizing these applications and what can we do to promote and support further utilization?". The members of the CCTI have experience asking and answering these types of questions and making use of the answers to further refine and improve existing applications. Evaluation approaches may involve (but not be limited to) field observations, focus groups, interviews, surveys, benchmark testing, usability assessments, bibliometric analysis, and usage log analysis. Further details of the CCTI evaluation plan can be found in the proposal's Evaluation and Tracking section.

### **Proposed Timeline for CCTI Implementation:**

Year 1: Establish Infrastructure, Begin Software Enhancement and Needs Assessments: Specific Aim 1 and 2: During the first six months of Year 1, the infrastructure for CTSI-wide software training and support will be established. This will include beginning the integration of existing CCTI and ICTRC (GCRC) training and support staffs and establishing communication plans. In Q2 needs analyses will begin in order to identify enhancements needed for the Clinical Trials Management Application (CTMA) to serve new users. In parallel, local instances of the caBIG tools for managing standard data and vocabulary, the Data Standards Repository (DSR), and the Enterprise Vocabulary Services (EVS) will be established, and researchers will be trained to use them. In the second half of the year, CTMA enhancements will be implemented, and any associated training materials developed. *Specific Aim 3:* The Online Research Community (ORC) project will begin with the recruitment and selection of personnel. A detailed project plan will be developed, and general responsibilities and resources will be allocated. In coordination with all stakeholders, appropriate milestones for the project

will be set, and CTSI community-wide committees for the governance, planning, and operation of the ORC will be formed. The needs and requirements of the OCR and its members will be assessed. In addition, various core audiences will be surveyed in order to prepare functional descriptions for the end-user accessible components. Appropriate controlled vocabularies for meta-tagging information in the ORC will be identified. The methods used will include, among others, contextual inquiry and contextual design. At the end of Year 1, a complete functional description of the end-user accessible OCR components and a clear understanding of the means to add Meta data to the content of OCR will have been defined.

Year 2: Software Needs Analysis, CTMA Rollout, and Grid Launch: *Specific Aims 1 and 2:* In Year 2, needs assessments will be focused in two areas: integration of CTMA with the clinical trials tools developed in the ICTRC, and integration of the existing caBIG/U Pitt tissue banking tools. CCTI will establish a grid node that is available to all CTSI participants by the middle of the year, and will begin extending standardized vocabulary services to UPMC. CTMA rollout will begin by the middle of Year 2, with the software made available for download through a GForge site and for query via the Grid. Throughout the year, CCTI will offer training for upcoming and released software along with ongoing software support and maintenance services. *Specific Aim 3:* In Year 2, detailed specifications based on the functional description will be developed. Furthermore, the system architecture will be developed, which includes researching and evaluating open-source software tools and preparing technical plans for writing “glue code” to connect separate tools. The specification for the Intelligent Information Routing Through an Ontology-Based Infrastructure will be written as well. At the same time, paper prototypes will be tested for human-computer interaction aspects using various contextual design and user testing methods. At the end of Year 2, detailed specification for the OCR components will be established, and a working system architecture allowing “plug-in” of the components will be completed.

Year 3: Continued Software Rollout and Integration: *Specific Aims 1 and 2:* By the end of Year 3, rollout of both CTMA and the Tissue Banking Tools suite will be complete. Most of the CTSI staff will have been trained in both the tools and in their use on the CTSI Grid. Before the end of Year 3, an additional caBIG tool will be added to the Grid. Software maintenance and support will be provided throughout the year, as the ICTRC and CCTI support staffs are more tightly integrated. *Specific Aim 3:* In Year 3, ORC specifications will be implemented. Tasks will include, among others, day-to-day project monitoring, pilot testing, and compliance testing. Furthermore, software licenses for electronic collaborative tools will be acquired. The first stage of the Customer Relationship Management (CRM) system, which will provide a tracking mechanism for interactions of scientists within the CTSI, will begin. At the end of Year 3, the OCR will be operational with some initial content, compiled mainly for pilot-testing purposes. Early adopters are expected to use the OCR on trial bases.

Year 4: Rollout of integrated clinical trial tools suite, addition of new grid tools, content accumulation and community formation: *Specific Aims 1 and 2:* In Year 4 both the integrated suite of clinical trial tools and at least two additional caBIG tools will be added to the CTSI Grid and rolled out to CTSI member with high-quality training and support. A major focus in Year 4 will be evaluation of the use and value of the Grid at CTSI, with the results made available to NIH early in Year 5. *Specific Aim 3:* While some content accumulation is already planned throughout the project period, the majority of the ORC content will be gathered in Year 4. Tasks will include the coordination of the information indexing process, formation of local extensions to the controlled vocabularies, and formal copy-editing of newly developed content. Surveys about the community forming process will be designed, conducted, and analyzed for evaluation purposes. The second stage of the CRM which will track interactions with offices and services within the CTSI will be developed. At the end of Year 4, comprehensive, information-rich directories of people, research interests, projects, services, funding opportunities, and other research-related entities will be in place. The intelligent information routing process will “push” information to and “pull” information from the community members. The education components of the OCR will be in use.

Year 5: Continued Evaluation and Spreading the Word: *Specific Aims 1 and 2:* By the end of Year 5, the CTSI Grid will be a well-established resource for CTSI researchers, and the software developed at CCTI will be available via GForge and the Grid. Training classes will be offered on a regular basis throughout the year. If the CTSA program authorizes it, the CCTI staff will begin the process of training other CTSA award sites to establish a similar infrastructure in their own environments. *Specific Aim 3:* With the help of the University Center for Social and Urban Research, surveys to evaluate all aspects of the OCR will be designed, conducted and analyzed. Methods used will be, among others, user surveys, utilization analyses, and outcomes measurement. The prepared data measuring outcomes metrics will be used to validate the evaluation process. Other tasks in Year 5 will include quality assurance of the indexing process and conceptualizing, authoring, and reviewing research reports and papers about the ORC. At the end of Year 5, a self-sustainable stable ORC, which can be handed over to the university IT support units for maintenance and necessary upgrades, will be in place. The underlying code and infrastructure will be maintained and provided as open source to all interested organizations.



**Literature Cited:**

1. NIH Roadmap for Medical Research page. Available at: <http://nihroadmap.nih.gov/>. Accessed March 1, 2006.
2. NIH Roadmap for Medical Research. Re-engineering the Clinical Research Enterprise: Clinical Research Networks and NECTAR Overview page. Available at: <http://nihroadmap.nih.gov/clinicalresearch/overview-networks.asp>. Accessed March 21, 2006.
3. National Cancer Institute. caBIG™: cancer Biomedical Informatics Grid™ page. Available at: <https://cabig.nci.nih.gov/>. Accessed March 21, 2006.
4. Phillips J, Chilukuri R, Fragoso G, Warzel D, Covitz PA. The caCORE Software Development Kit: Streamlining construction of interoperable biomedical information services. *BMC Med Inform Decis Mak*. 2006;6:2-13.
5. National Institutes of Health: Biomedical Information Science and Technology Initiative (BISTI). NIH Roadmap National Centers for Biomedical Computing page. Available at: <http://www.bisti.nih.gov/ncbc/>. Accessed March 21, 2006.
6. U.S. Department of Health & Human Services. Office of the National Coordinator for Health Information Technology (ONC) page. Available at: <http://www.hhs.gov/healthit/bios.html>. Accessed March 21, 2006.
7. Bolster C. National health IT initiative moves into action: an interview with David Brailer. *Healthc Financ Manage*. 2005;59:92-93.
8. The White House. Executive Order: Incentives for the Use of Health Information Technology and Establishing the Position of the National Health Information Technology Coordinator page. Available at: <http://www.whitehouse.gov/news/releases/2004/04/20040427-4.html>. Accessed March 21, 2006.
9. The White House. Transforming Health Care: The President's Health Information Technology Plan page. Available at: [http://www.whitehouse.gov/infocus/technology/economic\\_policy200404/chap3.html](http://www.whitehouse.gov/infocus/technology/economic_policy200404/chap3.html). Accessed March 21, 2006.
10. Becich MJ, Gilbertson JR, Gupta D, Patel A, Grzybicki DM, Raab SS. Pathology and patient safety: the critical role of pathology informatics in error reduction and quality initiatives. *Clin Lab Med*. 2004;24:913-943.
11. Hersh W. Health Care Information Technology: Progress and Barriers. *JAMA*. 2004;292:2273-2274.
12. Turisco F, Keogh D, Stubbs C, Glaser G, Crowley Jr WF. Current Status of Integrating Information Technologies into the Clinical Research Enterprise within U.S. Academic Health Centers: Strategic Value and Opportunities for Investment. *J Investig Med*. 2005;53:425-433.
13. BRIDG (Biomedical Research Integrated Domain Group) Project page. Available at: <http://www.bridgproject.org/>. Accessed March 15, 2006.
14. Becich MJ. The role of the pathologist as tissue refiner and data miner: the impact of functional genomics on the modern pathology laboratory and the critical roles of pathology informatics and bioinformatics. *Mol Diagn*. 2000;5:287-299.
15. The National Cancer Institute. NCI Cooperative Prostate Cancer Tissue Resource (CPCTR). Available at: <http://www.prostatetissues.org/>. Accessed March 21, 2006.
16. Melamed J, Datta MW, Becich MJ, Orenstein JM, Dhir R, Silver S, Fidelia-Lambert M, Kadjacsy-Balla A, Macias V, Patel A, Walden PD, Bosland MC, Berman JJ. The cooperative prostate cancer tissue resource: a specimen and data resource for cancer researchers. *Clin Cancer Res*. 2004;10:4614-4621.
17. Patel AA, Kadjacsy-Balla A, Berman JJ, Bosland M, Datta MW, Dhir R, Gilbertson J, Melamed J, Orenstein J, Tai KF, Becich MJ. The development of common data elements for a multi-institute prostate cancer tissue bank: The Cooperative Prostate Cancer Tissue Resource (CPCTR) experience. *BMC Cancer*. 2005;5:108.

18. Patel AA, Gilbertson JR, Parwani AV, Dhir R, Datta MW, Gupta R, Berman JJ, Becich MJ. More than a Tissue Bank – An Informatics Infrastructure for a Multi-Institute Biorepository: The Cooperative Prostate Cancer Tissue Resource Model. *BMC Cancer*. Submitted 2006.
19. The Pennsylvania Cancer Alliance Bioinformatics Consortium page. Available at: <http://www.pcabc.upmc.edu/main.cfm>. Accessed March 21, 2006.
20. Patel AA, Gilbertson JR, Showe LC, London JW, Ross E, Ochs MF, Carver J, Lazarus A, Parwani AV, Dhir R, Mohanty S, Beck JF, Liebman M, Garcia F, Prichard J, Wilkerson M, Herberman RB, Becich MJ, PCABC. A Novel Cross-Disciplinary Multi-Institute Approach to Translational Cancer Research: Lessons learned from Pennsylvania Cancer Alliance Bioinformatics Consortium (PCABC). *BMC Cancer*. Submitted 2006.
21. von Eschenbach AC, Buetow K. Cancer Informatics Vision: caBIG™. *Cancer Informatics*. 2006;2:22-24.
22. The National Cancer Institute. SPIN – Shared Pathology Informatics Network page. Available at: <http://spin.nci.nih.gov/>. Accessed March 21, 2006.
23. Gupta D, Saul M, Gilbertson J. Evaluation of a deidentification (De-id) software engine to share pathology reports and clinical documents for research. *Am J Clin Path*. 2004;121:176-186.
24. Gilbertson JR, Gupta R, Nie Y, Patel AA, Becich MJ. Automated clinical annotation of tissue bank specimens. *Medinfo*. 2004;11:607-610.
25. Mitchell KJ, Becich MJ, Berman JJ, Chapman WW, Gilbertson J, Gupta D, Harrison J, Legowski E, Crowley RS. Implementation and evaluation of a negation tagger in a pipeline-based system for information extract from pathology reports. *Medinfo*. 2004;11:663-667.
26. Patel AA, Gupta D, Seligson D, Hattab EM, Balis UJ, Ubright TM, Kohane IS, Berman JJ, Gilbertson JR, Dry S, Schirripa O, Yu H, Becich MJ, Parwani AV, Shared Pathology Informatics Network. Availability and quality of paraffin blocks identified by the Shared Pathology Informatics Network (SPIN): A Multi-institutional study. *BMC Cancer*. Submitted, 2006.
27. The National Cancer Institute. SPIN – Shared Pathology Informatics Network Content page. Available at: <http://spin.nci.nih.gov/SPIN/content>. Accessed March 21, 2006.
28. The National Cancer Institute. caBIG Tissue Bank and Pathology Tools (TBPT) Workspace PowerPoint page. Available at: [https://cabig.nci.nih.gov/workspaces/TBPT/TBPT\\_Sep\\_2005.ppt](https://cabig.nci.nih.gov/workspaces/TBPT/TBPT_Sep_2005.ppt). Accessed March 21, 2006.
29. Phillips J, Chilukuri R, Fragoso G, Warzel D, Covitz PA. The caCORE Software Development Kit: streamlining construction of interoperable biomedical information services. *BMC Med Inform Decis Mak*. 2006;6:2.
30. Warzel DB, Andonaydis C, McCurry B, Chilukuri R, Ishmukhamedov S, Covitz P. Common data element (CDE) management and deployment in clinical trials. *Proc AMIA Symp*. 2003;:1048.
31. Covitz PA, Hartel F, Schaefer C, De Coronado S, Fragoso G, Sahni H, Gustafson S, Guetow KH. caCORE: a common infrastructure for cancer informatics. *Bioinformatics*. 2003;19:2404-2412.
32. GATE - General Architecture for Text Engineering page. Available at: <http://gate.ac.uk/>. Accessed March 21, 2006.
33. The University of Pittsburgh Office of Clinical Research, Health Sciences. Clinical Research Informatics Service (CRIS) page. Available at: <http://www.clinicalresearch.pitt.edu/irs/services/CRIS/index.cfm>. Accessed February 23, 2006.
34. Yount RJ, Vries JK, Councill CD. The Medical Archival System: An information retrieval system based on distributed parallel processing. *Inf Process Manage*. 1991;27:379-389.

35. Cooper GF, Buchanan BG, Kayaalp M, Saul M, Vries JK. Using computer modeling to help identify patient subgroups in clinical data repositories. *Proc AMIA Symp.* 1998;;180-184.
36. Vries JK, Marshalek B, D'Abarno JC, Yount RJ, Dunner LL. An automated indexing system utilizing semantic net expansion. *Comput Biomed Res.* 1992;25:153-167.
37. Schleyer TK. Collaboratories: leveraging information technology for cooperative research. *J Dent Res.* 2001;80:1508-1512.
38. Schleyer TK, Forrest JL. Methods for the design and administration of web-based surveys. *J Am Med Inform Assoc.* 2000;7:416-425.
39. Schleyer TK, Teasley SD, Bhatnagar R. Comparative case study of two biomedical research collaboratories. *J Med Internet Res.* 2005;7:e53.
40. The National Cancer Institute. caCORE 2.0 Technical Guide page. Available at: [ftp://ftp1.nci.nih.gov/pub/cacore/caCORE2.0\\_Tech\\_Guide.pdf](ftp://ftp1.nci.nih.gov/pub/cacore/caCORE2.0_Tech_Guide.pdf). Accessed March 13, 2006.
41. McKibbin KA, Friedman PW, Friedman CP. Use of a MeSH-based index of faculty research interests to identify faculty publications: an IAIMSian study of precision, recall, and data reusability. *Proc AMIA Symp.* 2002;;514-518.
42. Friedman PW, Winnick BL, Friedman CP, Mickelson PC. Development of a MeSH-based index of faculty research interests. *Proc AMIA Symp.* 2000;;265-269.
43. The University of Pittsburgh Department of Pathology. Conference Access for Pathology Faculty and Residents page. Available at: <http://teleconference.upmc.edu/pathconf/>. Accessed March 9, 2006.
44. Butler, BS . Communities as Dynamic Collaborative Filters: Modeling Technology, Knowledge, and Structural Change in E-mail Based Online Communities. In: *Proceedings of the 4th International Conference on Organizational Learning and Knowledge*. London, Ontario, Canada; 2001.
45. Vredenburg, K, Mao, J-Y, Smith, PW, Carey, T. A survey of user-centered design practice. In: Tervenn L, ed. *Proceedings of the ACM CHI 2002 Conference on Human Factors in Computing Systems Conference*. New York, NY: ACM Press; 2002:471-478.
46. Raven, ME, Flanders, A. Using Contextual Inquiry to Learn About Your Audiences. *Asterisk.* 1996;20:1-13.
47. Beyer H, Holtzblatt K. *Contextual design: defining customer-centered systems*. San Francisco, CA: Morgan Kaufmann Publishers; 1998.
48. Markus, ML. Toward a "critical mass" theory of interactive media. In: Fulk J, Steinfeld C., eds. *Organizations and Communication Technology*. Newbury Park, CA: Sage; 1990:194-218.
49. Mjolsness E and DeCoste D. Machine learning for science: State of the art and future prospects. *Science.* 2001;293:2051-2055.
50. The University of Waikato Department of Computer Science. Weka Data Mining Software page. Available at: <http://www.cs.waikato.ac.nz/ml/weka/>. Accessed March 14, 2006.
51. Kaiser J. Genomic databases: NIH goes after whole genome in search of disease genes. *Science.* 2006;311:933.
52. Segal E, Shapira M, Regev A, Pe'er D, Botstein D, Koller D, Friedman N. Module networks: Identifying regulatory modules and their condition-specific regulators from gene expression data. *Nat Genet.* 2003;34:166-176.
53. Friedman N. Inferring cellular networks using probabilistic graphical models. *Science.* 2004;303:799-805.
54. Sachs K, Perez O, Pe'er D, Lauffenburger DA, Nolan GP. Causal protein-signaling networks derived from multiparameter single-cell data. *Science.* 2005;308:523-529.

55. The University of British Columbia Computer Science Department. The Software Packages for Graphical Models / Bayesian Networks Written by Kevin Murthy page. Available at <http://www.cs.ubc.ca/~murphyk/Bayes/bnsoft.html>. Accessed March 17, 2006.
56. Ranganathan S, Williams E, Ganchev P, Gopalakrishnan V, Lacomis D, Urbinelli L, Newhall K, Cudkowicz ME, Brown RH Jr, Bowser R. Proteomic profiling of cerebrospinal fluid identifies biomarkers for amyotrophic lateral sclerosis. *J Neurochem*. 2005;95:1461-1471.

## ***Transformation of Research*** **CTSI Participant and Clinical Interactions Resources (PCIR)**

The Participant and Clinical Interaction Resources (PCIR) Core is a cornerstone of translational research, supporting both “bench to bedside” and “bedside to clinic” investigations. The PCIR Core of the University of Pittsburgh Clinical and Translational Science Institute (CTSI) will build on successful models within current General Clinical Research Centers (GCRC), as well as the wider research community at the University of Pittsburgh, to transform the current concept of participant and clinical interaction resources. Transformations include:

- Expanding the concept of PCIR to include community-based resources, building on several successful models among current investigators at the University of Pittsburgh;
- Encouraging further specialization of PCIR facilities to better meet a range of investigator needs, using current GCRC components and new PCIR Core components as models;
- Reducing barriers to investigators, particularly young investigators, who would benefit from using the PCIR Core, through more efficient scientific review and administrative processes; and
- Developing a comprehensive plan to assess evolving investigator needs for research resources and the adequacy of existing resources in meeting those needs.

To accomplish these transformations, the following **Specific Aims for the PCIR Core** have been defined:

1. To provide a range of participant and clinical interaction resources that support translational patient-oriented research in a variety of settings, including specialized research care settings at the University of Pittsburgh Medical Center (UPMC) main campus and community-based settings.
2. To coordinate participant and clinical interaction resources by using efficient administrative structures for scientific review, participant safety, resource allocation, and management.
3. To develop additional resources for participant and clinical interactions through collaboration with the CTSI Center for Clinical and Translational Informatics (CCTI). The PCIR Core will provide a platform for innovation in translational informatics in research data management, scientific review, and research administration. The ultimate goal is to ensure adequate and appropriate informatics support wherever a study is conducted.
4. To provide resources that support the research activities of junior faculty and trainees enrolled in CTSI training programs.
5. As part of the CTSI Tracking and Evaluation Plan, to develop qualitative and quantitative processes for comprehensively evaluating investigator needs for PCIR, and the performance of the Core in meeting those needs.

## **BACKGROUND**

**Participant and Clinical Interaction Resources are a critical component of the Clinical and Translational Science Institute.** PCIR can be viewed as one of the effector pathways of the CTSI. The training and education, intellectual capital, and novel methodologies that go into developing a protocol must ultimately be translated into the collection of participant data. PCIR constitute those data collection resources. While it is certainly possible for individual investigators to develop their own data collection resources, there are numerous advantages to having coordinated PCIR as a component of the CTSI:

- Efficiency of resources and economy of scale. Clinical research procedures are often quite complex, both from the perspective of complicated procedures and the use of specialized equipment. Sharing procedural expertise and equipment can lead to greater standardization, improved quality control, and reduced costs.
- Skills of dedicated, research-focused personnel. The procedures and equipment described above require highly-trained research personnel. These personnel are the most important resource of the PCIR Core. Dedicated research nurses and other staff have specialized training in data collection, data integrity, and protection of human subjects and do not have the competing demands of clinical responsibilities.
- Intensity of research procedures. Clinical and translational research procedures can be as simple as collecting questionnaire data, as complex as conducting gene therapy protocols, or anything in between. For

protocols requiring more complicated or high-intensity procedures, a dedicated inpatient hospital environment or other specialized research facility is essential.

- **Specialized research centers.** The range of clinical and translational research activities conducted at the University of Pittsburgh is quite broad. Specialization in areas such as women's health, oncology, or sleep and circadian rhythms benefits from specialization in research facilities, which the PCIR Core will provide.
- **Efficient conduct of clinical and translational research in the community.** Traditional GCRCs are centered on hospital-based facilities, and have provided one successful model for clinical and translational research. However, an increasing amount of clinical and translational research is also conducted in the community. The same arguments regarding efficiency and staff skills apply to research conducted in these environments. A major focus of the University of Pittsburgh CTSI will be to develop community-based participant and clinical interaction resources ranging from a more traditional hospital-based research center to physician offices and specialized outpatient research offices.
- **PCIR create a focus for interaction of other CTSI resources.** Specialized research facilities are a nexus for other components of the CTSI. Interaction with the Center for Clinical and Translational Informatics is a critical component in the efficient operation of the PCIR Core, contributing to functions such as management of protocol reviews, resource utilization, data collection, and data management. PCIR are also an extremely valuable resource for the educational mission of the CTSI, providing protocol review and data collection resources to investigators with little independent funding. The PCIR Core will also provide access to community-based research that would be difficult for many investigators to access otherwise. In similar ways, the PCIR Core will enhance the activities of other CTSI components, including Pilot and Collaborative Translational and Clinical Studies (serving as a resource for new investigators and studies); Community PARTners Program (providing a presence for research in the community); Translational Technologies and Resources (which will use data collected in the PCIR Core); and Development of Novel Clinical and Translational Methodologies (again, as a resource for conduct of protocols and data collection).

**Participant and Clinical Interaction Resources build upon a strong foundation from the University of Pittsburgh General Clinical Research Centers (GCRCs).** The PCIR Core benefits from a long history of innovation and success at the University of Pittsburgh GCRCs, including the University of Pittsburgh Adult GCRC and Children's Hospital of Pittsburgh Pediatric GCRC. These GCRCs include a variety of innovative resources that support clinical and translational research.

#### **University of Pittsburgh Adult GCRC:**

**History and trends.** The adult GCRC comprises four clinical centers, three core laboratories, and resources for informatics, biostatistics, and education (Figure 1). The GCRC is currently operating in its 44<sup>th</sup> consecutive year of funding and has undergone a dramatic expansion in scope and resources over the past ten years under the leadership of Program Director Robert Branch, MD, who now serves as a Co-Director of the CTSI. The number of GCRC research beds has almost doubled, three new clinical sites were added, and three new core labs added. Also during this time, complementary educational resources have been developed at the University of Pittsburgh through the K30 and K12 educational programs. GCRC-based informatics and biostatistical resources have also been developed. Over the past 10 years, the number of outpatient research visits has tripled, while the number of inpatient visits has held steady at approximately 1000 per year. In recent years a new visit type, the Offsite Research Visit, has been added and is currently used as a means of studying subjects in their homes. The GCRC enjoys the strong support of the University of Pittsburgh Schools of the Health Sciences, UPMC, and the departments which host each of the GCRC facilities. For instance, major renovations have been undertaken in GCRC facilities at Western Psychiatric Institute and Clinic (WPIC) and Magee-Womens Hospital (MWH), and a \$2.2M renovation is currently ongoing for the Montefiore University Hospital (MUH) GCRC. The success of the GCRC is highlighted by the fact that it is one of the nation's 10 largest, and by its outstanding priority score of 143 during its last peer review in 2003.

**Current resources and structure.** Clinical centers in the adult GCRC include the MUH-GCRC; a satellite facility located at the University of Pittsburgh Cancer Institute (UPCI); the MWH Clinical Research Center (MWH-CRC); and the Clinical Neuroscience Research Center (CNRC) located at WPIC. Centers supported by the GCRC include an Information Technology and Biostatistics Core (ITBC) and an Education Core that hosts the Clinical Research Feasibility Fund (CRoFF), Mentored Medical Student Clinical Research (MMSCR) and summer medical student programs. The GCRC also supports three core laboratories: the Pharmacogenetics Core Laboratory (PCL), the Positron Emission Tomography Radiochemistry Laboratory (PETRCL), and the Sleep and Circadian Rhythms Laboratory (SCRL).

**Productivity.** The productivity of the adult GCRC as a whole is summarized in Table 1.

**Research highlights.**

**MUH-GCRC:** The obesity epidemic facing Western countries has produced an urgent need to understand the mechanisms of obesity-related morbidities and the effects of interventions. MUH-GCRC investigators are examining the role of mitochondrial dysfunction in the pathogenesis of insulin resistance in type 2 diabetes mellitus, obesity and aging.

Physiological studies in these groups indicate lower reliance on fat oxidation in association with reduced capacity for oxidative phosphorylation, altered morphology and sub-cellular distribution of muscle mitochondria and accrual of fat within muscle. GCRC investigators have also developed novel methods for quantifying fat content within human skeletal muscle in vivo using magnetic resonance imaging. Muscle biopsy studies following weight loss and exercise interventions in obese subjects have demonstrated a surprising increase in intramyocellular lipid, concomitant with an increased oxidative enzyme capacity and an increased reliance on fatty acid oxidation as an energy substrate. The intervention was also associated with a 49% improvement in insulin sensitivity.<sup>1,2</sup>

**MWH-CRC:** The Prenatal Exposure and Preeclampsia Program Project Grant has utilized the CRC to obtain samples for nested case controls. This study has demonstrated striking evidence of endothelial cell activation before clinically evident preeclampsia, which previously was conceptualized as a hypertensive disorder. Recently, the hypothesis that oxidative stress may be responsible for altering endothelial function has been tested and supported. As a result, trials of antioxidant therapy with Vitamin C and E have been designed and subsequently funded by the NICHD and NHLBI.<sup>3-5</sup>

**CNRC:** Sleep disturbances are a common feature of psychiatric and medical disorders, as well as primary sleep disorders. However, little is known about the potential neural mechanisms underlying such disturbances. Led by Eric Nofzinger, MD, investigators at the CNRC have used [<sup>18</sup>F]-FDG PET studies to study regional brain metabolism during different stages of sleep and wakefulness in patients with depression, insomnia, and healthy aging. They reported the first published studies showing altered patterns of glucose metabolism during sleep in these groups, which indicate a pattern of “hypermetabolism” relative to healthy young subjects. Understanding the pathophysiology of sleep disturbances can lead to improved and more targeted interventions.<sup>6-8</sup>

**Children’s Hospital of Pittsburgh GCRC (CHP-GCRC):**

**History and trends.** Children’s Hospital of Pittsburgh (CHP) is among the foremost pediatric hospitals in the country. Patient-oriented research in pediatrics was formalized when the CHP-GCRC opened in 1962. Silva Arslanian, MD has served as Program Director since 1999. In the 43 years since its inception, the GCRC has provided critical leadership in pediatric patient-oriented research, research training and the protection of human subjects. Institutional commitment to pediatric research at CHP and the University of Pittsburgh is strong. As part of the recruitment of David Perlmutter, MD to become Chair of the Department of Pediatrics, CHP committed \$15.4 million and renovation of an additional 28,000 square feet of research space. The merger of CHP and UPMC in 2001 committed \$250 million to pediatric research and new clinical programs over the next 10 years. As part of the merger, a new children’s hospital and a new pediatric research building are being built, constituting a \$575 million construction project due to be completed in 2008. The new hospital will include 3,500 square feet dedicated to a pediatric core for clinical translational research. Additional ambulatory clinical space and office space are being programmed for the CTSI pediatric core. The new research building will include 230,000 square feet with the capacity for approximately 80 investigators and their laboratories.

**Current resources and structure.** The current CHP-GCRC consists of a four-bed patient facility located on a 28-bed combined unit with a general older child and adolescent pediatric ward. The GCRC has priority for scheduling up to 4 research beds for inpatient protocols on this unit. GCRC inpatient and outpatient areas, specimen processing laboratory, DEXA facility, administrative offices, and nursing offices are located adjacent to each other, enhancing the efficiency of the research enterprise. The GCRC also provides support for both Informatics and Biostatistics. The administrative structure of the GCRC is shown in Figure 1.

**Table 1: Productivity of the Adult GCRC, 2005**

Active research protocols	226
Investigators	104
Divisions/departments with GCRC protocols	26
Schools with GCRC protocols	Medicine, Nursing, Pharmacy, Public Health, Health & Rehabilitation Sciences
Research subjects	5,909
Research visits	13,617 Outpatient, 337 Inpatient, 876 Scatter bed days, 367 Offsite Research Visits

**Productivity.** The productivity for the CHP-GCRC in 2005 is summarized in Table 2.

**Research highlights.**

**Type 2 Diabetes in Youth.** The past decade has witnessed an emerging epidemic of childhood type 2 diabetes. CHP-GCRC supported studies have demonstrated that: 1) Obesity; minority ethnicity and race; family history of type 2 diabetes; and conditions associated with insulin resistance are major risk factors for youth-onset type 2 diabetes; 2) The pathophysiology of type 2 diabetes in youth includes both insulin resistance and impaired insulin secretion, the latter being more severe than that observed in adults; 3) The progressive loss in  $\beta$ -cell dysfunction appears to be three times faster than that observed in adults; and 4) Youth with type 2 diabetes have evidence of early cardiovascular disease, manifest in increased arterial stiffness commensurate with values in 50 year old men.<sup>9,10</sup>

**Silent brain injury** has been identified in infants using serum biomarkers, namely neuron specific enolase and myelin basic protein. This approach identified several cases of putative inflicted childhood neurotrauma from abuse and may represent an exciting new tool to aid pediatricians in the often difficult diagnosis of shaken baby syndrome.<sup>11</sup>

**Results from investigator focus groups have provided feedback on how to improve PCIR at the University of Pittsburgh.** In preparation for this application, two focus groups were held for investigators involved in clinical and translational research. One group focused on current GCRC users, and the other group on investigators with little or no GCRC experience. The 14 participants ranged in rank from Assistant to full Professor and represented four schools within the University. Investigators were asked to describe their current research, aspects of the GCRC they found useful, barriers they found within the GCRC system, and other types of resources they would find useful. A surprising degree of consistency emerged from both groups. Major themes included the following:

- The GCRCs were cited as providing a set of valuable resources, including dedicated space, skilled staff, and resources for off-site research visits. Several investigators share staff responsibilities with the GCRC.
- Investigators need broader access to community-based research resources, including dedicated research space and personnel in the community. Several variants were discussed, including wider use of UPMC hospital and physician networks for research studies, community-based research centers, mobile research units, and organized transportation from communities to UPMC facilities.
- Investigators had strong feelings about reducing administrative barriers to clinical and translational research. For instance, the multi-layered process of scientific and human subjects review was described as “onerous,” time-consuming, and bureaucratic. One perception was that investigators feel they are “there to serve [the bureaucracy] rather than the other way around.”
- There was a near-universal call for better access to data management, statistical support, and recruitment resources, particularly among junior investigators.
- Administrative assistance in negotiating with UPMC (for instance, on research rates for clinical tests and procedures) was requested by several investigators.
- There was a clear need for improved communication regarding research resources, including but not limited to patient care facilities. For instance, some investigators cited difficulties discovering what research group might be willing to collaborate on certain research procedures.

Even though these focus groups included only a small sampling of investigators, the provided feedback has been invaluable. The themes identified are entirely consistent with the themes to be developed in the PCIR Core and other core resources of the CTSI. Thus, from this feedback as well as the assessments of the broad research community participating in the CTSI, several key opportunities for transformation have been identified:

- Systematic evaluation of investigator needs for participant and clinical interaction resources, for the express purpose of designing and implementing enhancements to PCIR
- Improved investigator awareness and access to a wider range of PCIR
- Reducing barriers to investigators, specifically with regard to scientific and administrative review

**Table 2: Productivity of the CHP-GCRC, 2005**

Active research protocols	73
Current Investigators	41
Divisions/ departments with GCRC protocols	9 Departments, 17 Divisions
Schools with GCRC protocols	Medicine, Nursing, Dentistry, Behavioral sciences, Public Health, Engineering
Research subjects	1,445
Research visits	206 inpatient, 59 scatter bed days and 1,612 outpatient visits



- Improved coordination and management of resources
- Broader use of informatics throughout the conduct of research
- Improved access by junior investigators and trainees

## CORE DESIGN AND METHODS

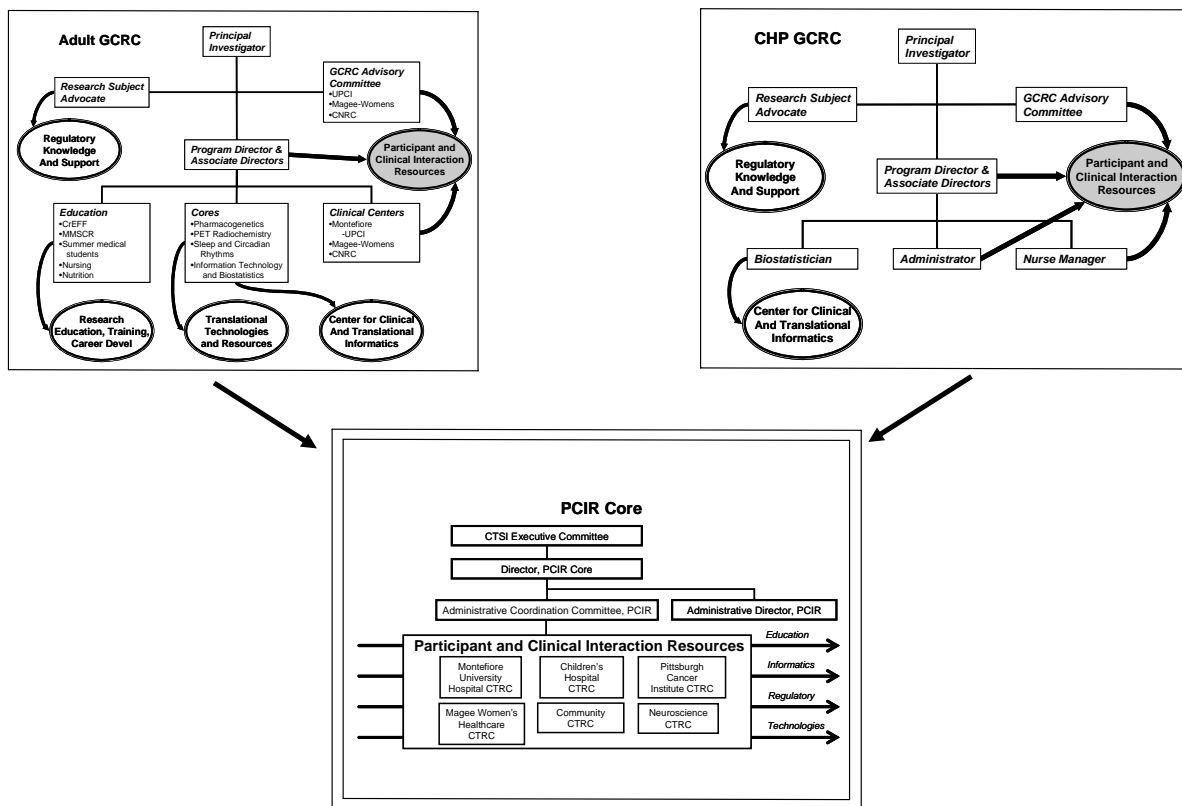
**Overview: What transformations will be made?** As described above, the GCRCs have been very productive in conducting clinical/ translational research and in training young investigators, but they exist within a program format that is over 40 years old. Through the new CTSI, several opportunities to transform the GCRCs into even more relevant, widely used participant and clinical interaction resources for clinical and translational research present themselves. These transformations will impact not only bench-to-bedside translational research, but bedside-to-community research as well. Major transformations will include:

- Systematic evaluation of investigator needs. The GCRCs have traditionally provided hospital-based research services to investigators; if a particular investigator could use these services, s/he would apply to the GCRC. Unfortunately, this system may neglect the types of services and resources that investigators would find most useful. The new PCIR Core will institute a model that begins with an assessment of investigator needs in clinical and translational research, then develop and modify resources to meet those needs. In this effort, the Tracking and Evaluation resources of the CTSI will be utilized.
- Improved investigator awareness and access to a wider range of PCIR. Although the GCRCs serve a large number of investigators, they still represent only a fraction of the investigators conducting clinical and translational research at the University of Pittsburgh. The success of the existing GCRCs can be transformed by expanding their scope and utilization. Improved access begins with education of trainees, but also involves a major educational effort within the current investigator community, and continues through the efforts of CTSI research managers. Thus, efforts in this area will be coordinated with the Research Education, Training, and Career Development and the Pilot and Collaborative Translational and Clinical Studies components of the CTSI. Furthermore, although the current GCRCs offer centralized, specialized research facilities, many investigators have developed other research resources outside of the GCRCs. By taking advantage of the opportunity to develop PCIR resources in the community, the PCIR core will minimize inefficiency and expense, while making additional resources available to junior investigators and those not currently involved in community-based research.
- Improved coordination and management of resources. By having centralized CTSI Research Facilitators with knowledge of all CTSI resources, including PCIR, investigator needs will be better match to existing resources, thereby achieving more efficient resource utilization. In addition, some current administrative procedures within GCRCs are inefficient, resulting from conflicting requirements of the National Center for Research Resources (NCR), the University of Pittsburgh, and UPMC (for example, with regard to cost accounting). Within the CTSI, administrative procedures will be streamlined to help reduce costs and devote more resources to actual research. In addition, a direct reporting line between the PCIR Core and the central administration of the CTSI will be instituted. This high-level oversight by the CTSI Executive Committee will allow resources to be assigned and transferred among the PCIR core resources depending on current utilization and investigator need.
- Using PCIR sites as independent models for specialized clinical and translational research. While there is clearly a need for general clinical research resources, there are also increasing pressures for more specialized clinical and translational research resources, and for resources in close proximity to patient care sites. Over time, the various GCRC facilities at the University of Pittsburgh have developed distinct identities and research missions; however, they have been constrained by needing to fit within GCRC guidelines. Under the CTSI, the more specialized resources, such as women's health research and community-based research will be extended. The different PCIR sites can thus serve as distinct models of how to conduct clinical and translational research, which will improve service to the research community. In addition, such experimentation with different models of PCIR will enable the development of the most efficient overall system. At the same time, simplified administrative and reporting requirements will allow scarce resources to be devoted to actual research support.
- Broader use of informatics. The current GCRC Information Technology and Biostatistics Core has collaborated with Michael. Becich, MD, PhD and colleagues in the Department of Biomedical Informatics to develop several GCRC tools, such as systems for participant scheduling, protocol management, and data management. Under the aegis of the CTSI, opportunities and resources for translational informatics will

become available to a broader community of researchers. In addition to managing resources of the PCIR Core, an increased role for translational informatics in data management, particularly for trainees and junior investigators with limited resources, is envisioned.

The transformation of existing GCRC resources into PCIR within the University of Pittsburgh CTSI is illustrated schematically in Figure 1. The PCIR Core is expected to act as a “meeting place” for various components of the CTSI to come together and interact around the collection of clinical and translational research data.

**Figure 1: Transformation of GCRCs into the CTSI Participant and Clinical Interaction Resources Core**



**Organizational structure.** One of the major challenges of transforming the current GCRC structure into the new PCIR Core of the CTSI will be to encourage sufficient independence and innovation within each component in order to meet investigators’ needs, while simultaneously providing the structure and coordination needed to facilitate efficient management. The administrative structure proposed for PCIR, shown in Figure 1, will serve these two important goals.

The PCIR Core is composed of six distinct Clinical and Translational Research Centers (CTRCs). The Core and the individual CTRCs interact with other resources of the CTSI, including most importantly the Research Education, Training, and Career Development Core, the Center for Clinical and Translational Informatics, the Regulatory Knowledge and Support Core, and the Translational Technologies and Resources Core. The expertise from these cores will culminate in the development of protocols that will be implemented through the PCIR Core.

Daniel J. Buysse, MD, **Director of the PCIR Core**, will be responsible for overall program direction and implementation of the Specific Aims. He will represent the PCIR Core as a member of the CTSI Executive Committee, reporting directly to the CTSI Director, Steven Reis, MD. Dr. Buysse will exercise oversight of the CTRC Program Directors and PCIR Core Administrative Director, chair quarterly meetings of the PCIR Administrative Coordination Committee, interact with other cores of the CTSI, oversee the recruitment plan for new investigators and protocols, and develop new CTRC initiatives. He will be assisted in all duties by the **PCIR Core Administrative Director**, Dawn G. Stocker, MPA. Ms. Stocker will oversee operations of the CTRCs, monitor resource usage, review personnel and fiscal resources, and interact with other supporting

entities including the University and UPMC. She will serve a project management role, maintaining information flow among and between CTRCs and central administration, managing logistics, implementing program initiatives, and ensuring programmatic compliance. Ms. Stocker will be assisted in fiscal administration by a **Financial Administrator**, Rosemary Sabol, MBA. Ms. Sabol will be responsible for ensuring that sound billing and financial recording-keeping mechanisms are in place at all PCIR locations. She will also be responsible for routine monitoring of all CTRC expenditures, billing practices and timeliness, and financial reporting.

Dr. Buysse, assisted by the Administrative Director, will chair quarterly meetings of the **PCIR Administrative Coordination Committee**. This committee will consist of CTRC Program Directors and Administrative Managers. The meetings will be used to evaluate the success of the PCIR Core in achieving its Specific Aims. In particular, the committee will review progress on meeting investigators' evolving needs and providing access to participant interaction resources. Additional topics will include: Review of new protocols approved by CTRCs; discussion of issues pertaining to participant health and safety; review of fiscal and other administrative issues of common interest to the different CTRCs; discussion regarding the distribution of research activities and resources across the CTRCs; and updates from other CTSI Cores. Finally and most importantly, new program direction and interaction with other CTSI cores will be vetted.

Each of the CTRCs and clinical cores will be managed by a **Program Director**, an **Administrative Manager** (or the PCIR Administrative Director), a **Clinical Manager**, and a **Scientific Review Committee Chair**. Within each CTRC, the individuals in the leadership positions will meet monthly or bi-monthly to coordinate research activities, discuss problems, set programmatic directions, and review fiscal and administrative issues. Written meetings notes will be submitted to the PCIR Core Director. Table 3 indicates the leadership for each of the CTRCs.

Table 3: Administrative Leadership of CTRCs

CTRC	Program Director	Administrative Manager	Clinical Research Manager	Scientific Review Committee Chair
Children's Hospital CTRC	Silva Arslanian, MD	Lynette Orlansky, BS	Janet Bell, RN	Ellen Mandel, MD
Magee-Womens Hospital CTRC	Judith Balk, MD	Patricia Barcic, RN, BSN	Patricia Barcic, RN, BSN	Bryna Harwood, MD, MS
Montefiore University Hospital CTRC	Robert Branch, MD	Dawn G. Stocker, MPA	Jill Huwe, BSN	Trevor MacPherson, MD
University of Pittsburgh Cancer Institute CTRC	Kenneth Foon, MD	Dawn G. Stocker, MPA	Gail Tribble, RN, BSN	Samuel Jacobs, MD & Suresh Ramalingam, MD
Neuroscience CTRC	Daniel Buysse, MD	Dawn G. Stocker, MPA	Lisa Oross, BSN	J. Richard Jennings, PhD
Community CTRC	Susan Greenspan, MD	Dawn G. Stocker, MPA	Gail Tribble, RN, BSN	TBN

- The **CTRC Program Directors** are active translational research faculty members who have experience in administering large programs of research. Their major duties will be to identify research needs and opportunities for the CTRC; to promote use of the CTRC by the investigator community; to oversee the implementation and safe and efficient conduct of research protocols, to ensure compliance with regulations and safety standards; and to oversee the management of budget and personnel resources.
- The **CTRC Administrative Managers** are experienced research and clinical administrators. Their major duties will be to manage the CTRC budget; to oversee personnel and human resource matters; to ensure efficient scientific review; and to assist the Program Director in fulfilling all of his/her duties. Administrative Managers will have a parallel reporting relationship with the Core Administrative Director.
- The **CTRC Clinical Managers** will be research nurses or similar personnel who have experience conducting clinical and translational research in human subjects. Specific qualifications for the Clinical Managers will depend on the specific research focus of their CTRC. In all cases, however, the Clinical Manager will be responsible for translating the research protocol into accurate and efficient data collection procedures, and for supervising the staff who conduct those procedures. In doing so, the Clinical Managers will collaborate with investigators and investigators' research teams to ensure the well-being of research participants, including their safety, health, and privacy.
- The **Scientific Review Committee Chair** of each CTRC will be responsible for the scientific review of each CTRC research protocol. They will recruit committee members, assign reviewers, run Scientific Review meetings, and review health and safety concerns with research protocols. If questions about health and safety arise, the Scientific Review Committee Chair will be responsible for communicating with the IRB. Finally, the Scientific Review Committee Chair will represent the Scientific Review Committee in advising the Program Director about potential new directions for the CTRC.

**Specific activities of the PCIR Core.** The following section describes how the PCIR Core and its constituent CTRCs will accomplish their Specific Aims. Some of these activities will represent activities of the PCIR Core as a whole, and others will be the responsibility of the individual CTRCs.

**Specific Aim 1: To provide a range of participant and clinical interaction resources that support translational patient-oriented research in a variety of settings, including specialized research care settings at the UPMC main campus and community-based settings.** Accomplishing Specific Aim 1 will be the mutual responsibility of the PCIR Core as a whole, under the leadership of the Core Director, and of the individual CTRCs, under the leadership of the individual Program Directors. Specific Aim 1 subsumes all of the major resources and personnel of the PCIR Core. Two major types of PCIR facilities are proposed: University-based CTRCs and Community-based CTRCs. In addition, the PCIR Core will help to coordinate other clinical and translational research core resources at the University.

University-based CTRCs. These facilities will be closest in function to existing GCRC resources. However, with the advent of the CTSI, each facility will be able to differentiate to a greater extent, in order to fulfill more specialized research functions and develop efficient operations.

- The *Montefiore University Hospital CTRC* will serve as a model of a research “intensive care” unit, conducting both inpatient and outpatient studies that require a high degree of nursing intervention, monitoring, and complex research procedures. Typical studies conducted in this CTRC will include hyperinsulinemic glucose clamp studies, muscle biopsy studies, and pharmacokinetic studies. Unit staff also have the capability of supporting research procedures (e.g., phlebotomy) throughout the inpatient units of Presbyterian and Montefiore hospitals.
- The *Magee-Womens Hospital CTRC* will serve as a model for women’s specialty clinical and translational research. A unique feature of Magee is that it serves both as an inpatient facility and a large ambulatory care center where women receive complete health care, not simply reproductive and gynecologic care. For instance, Magee hosts women’s lupus and cardiovascular centers, and has recently become home to the UPMC obesity surgery program.
- The *Neuroscience CTRC* has specialized facilities and equipment for conducting human neuroscience studies, with a focus on sleep and circadian rhythms. The facility includes two time isolation apartments, where studies up to 15 days’ duration have been conducted, and manages equipment for conducting in-home sleep studies. This CTRC also conducts more general physiological monitoring and clinical procedures in neuropsychiatric patients.
- The *Children’s Hospital CTRC* focuses on inpatient and outpatient research in children and adolescents, taking into account the specialized pediatric facilities, staff, and procedures needed for this population. The CHP-CTRC will serve as the nidus for a children’s research network, encompassing a full range of clinical and translational research.
- The *University of Pittsburgh Cancer Institute CTRC* focuses on clinical trials and translational research related to oncology. The main emphasis of this facility is on specimen collection, drug infusions, and pharmacokinetic studies. Selected studies also require research nursing support for patients admitted as inpatients to Shadyside Hospital but enrolled in investigational studies. This CTRC will operate in conjunction with the University of Pittsburgh’s NCI-funded cancer institute.

Community CTRC. The Community CTRC will include three distinct components: Community hospital-based CTRC, Community practice-based CTRC, and Community center-based CTRC. The Community CTRC will play a critical role in transforming clinical and translational research at the University of Pittsburgh, by making community-based resources more widely available to investigators. Rather than focusing on a particular research theme, these units will focus on access to populations traditionally under-represented in University-based clinical and translational research. The resources within this CTRC are viewed as pilot projects for extending the scope of clinical and translational research into the community. As such, these resources will undergo development and modification over time, in order to best meet investigator needs. The Community CTRC will interact with and build on existing models for community-based research developed by investigators at the University. It will also interact extensively with resources described in the Community PARTners

(Partnering to Assist Research and Translation) Program of the CTSI. The viability of the Community CTRC is based on the strengths of UPMC, one of the largest not-for-profit integrated health care systems in the United States and the leading health care delivery system in western Pennsylvania. UPMC employs over 35,000 employees and 5,000 physicians working in 19 hospitals and 400 outpatient sites, with more than 3M annual outpatient visits in 29 western Pennsylvania counties.

- A Community hospital-based CTRC model will be used to focus CTSI efforts on the identification of mechanisms for and reduction of racial health disparities. The *CTSI Braddock Minority Health CTRC* will be developed at the UPMC Braddock Hospital in Braddock, PA, a traditionally African American Community just outside of Pittsburgh. This CTRC will provide five patient rooms (240 sq. ft. each, plus adjacent corridor space = approximately 2000 sq. ft. total) on inpatient Unit 4 West, which will be available for both higher and lower-intensity research studies (see letter of support: President, UPMC Braddock). The research unit at UPMC Braddock will be staffed with nurses and staff from the University-based CTRCs on a limited number of days per month. The unit will also be available for use by the staff of specific research studies who wish to recruit and study subjects at this site on a scheduled basis. UPMC Braddock will develop plans to assist in recruitment of participants for CTSI studies. After establishing experience at Braddock, the feasibility of developing similar relationships that target specific populations (e.g., rural; aging) at other UPMC hospitals within the 29 county region of Western Pennsylvania will be investigated.
- The *Community practice-based CTRCs* will be modeled on successful collaborations developed by investigators such as Charles F. Reynolds III, MD from the Department of Psychiatry and Susan L. Greenspan, MD from the Department of Medicine. Formed in 1994, Community Medicine, Inc. (CMI) is a network of over 100 physician practices owned by UPMC. Although the large majority of these practices are community-based and non-academic, CMI is committed to support research on problems relevant to the practice of primary care medicine. CMI has identified a subset of practices among its 75 primary care practices whose physicians were interested in collaborating in the conduct of clinical research. These practices include 15 urban or suburban internal medicine and family medicine practices in the greater Pittsburgh region with a total of 77 PCPs serving approximately 64,800 unique patients. The success and productivity of the relationship between University investigators and CMI has been facilitated by several ingredients, including: 1) A shared commitment to solving prevalent health problems in general medical settings; 2) Development of screening, assessment, and chronic disease management strategies that fit in well with office culture and practice; 3) Periodic feedback to primary care colleagues about the progress of studies; 4) Early consultation with primary care colleagues on the focus and design of studies; 5) Monetary compensation to cover the costs of operating in the practices (shared office space, mailing, record keeping); and 6) Working closely with practice managers to ensure smooth operation of the research. The results of University-CMI collaborations have been landmark peer-reviewed publications in high-impact journals such as JAMA<sup>12</sup>, NEJM<sup>13</sup> and JCEM<sup>14</sup>. Thus, the University of Pittsburgh-CMI collaboration represents a valuable model for the CTSI. The practice-based CTRC will also be linked to the “Evidence-Based Practice in Community Care” project in the Community PARTners Program.
- A model for a *Community center-based CTRC* is the Department of Epidemiology Satellite Research Clinic which is located in Monessen, PA. This clinic was established in 1986 by Jane Cauley, Dr.Ph, MPH and colleagues from the Graduate School of Public Health. Monessen is a rural, non-farm setting approximately 30 miles from the main campus of the University of Pittsburgh. The Monessen Clinic has been involved in both observational studies and randomized clinical trials. Most of the research has focused on osteoporosis, reflecting the primary interest of Dr. Cauley and her colleagues, but this model satellite clinic has been adapted for use by other types of investigations; NIH-funded studies run out of the clinic have focused on areas as diverse as sleep disorders, macular degeneration, ApoE and lipoproteins, and oral health risk. Current research staff includes a clinic manager, two nurses, two medical assistants, a laboratory manager, five or six research and data assistants, and two van drivers. Investigators at the University of Pittsburgh provide medical oversight for the research studies, and nurse practitioners from the Community Health Center are used for the medical history and physical exams. The clinic offers door-to-door van service by leasing vans/vehicles from the University of Pittsburgh motor pool, which includes maintenance and insurance. The clinic is housed in 4,000 square feet of rented office space and includes seven examination rooms, 12 staff offices, two data offices, a kitchen and restroom, laboratory, and storage rooms. Thus, the staffing and space of the Monessen Clinic is actually quite similar to that of a traditional GCRC. Home visits have been part of all longitudinal studies and include procedures such as phlebotomy, assessment of bone

quality using ultrasound, physical function (gait, chair stands, strength), and polysomnography. For protocols that require medical testing not available at the clinic, the clinic has negotiated NIH research rates with the Monongahela Valley Hospital and private practice groups. The six largest studies conducted at Monessen Clinic have recruited over 28,000 subjects and conducted over 51,000 initial research visits. Retention rates are excellent, averaging well above 95%. Finally, the Monessen Clinic has served an important educational function; 13 PhD students from the Department of Epidemiology have completed their doctoral research using this facility. The CTSI will collaborate with Dr. Cauley and colleagues to use the Monessen Clinic as a data collection site for other University of Pittsburgh research studies. Costs will be shared between the CTSI and the individual research study for resources used at the clinic.

Using the Monessen Clinic as a model, the feasibility of renting space in other community settings, such as the Urban League of Pittsburgh or other geographically diverse areas in and around Pittsburgh, will be explored. Sites will be selected based on their unique demographics and relatively low penetration of University of Pittsburgh/UPMC activities. The PCIR planning process for this model will benefit from the CTSI evaluation of the use of the Urban League as a site for development of a “research-informed” community in the CTSI Community PARTners Program. Although our specific model for community center-based research will undergo further development, our working model includes three types of activities: 1) A continuity screening clinic staffed by a PCIR Core nurse; 2) Informational talks given by investigators who wish to recruit participants with specific health conditions; and 3) Research studies, using the site as shared space for conducting community-based research, focusing mainly on studies that require simple research assessments such as demographics, questionnaires, and blood/urine samples.

- The feasibility of *other community-based research resources* will be investigated through pilot studies in the PCIR Core. One resource commonly requested by investigators is *coordinated transportation* for research participants from the community to central UPMC sites. Because of geographic, economic, and cultural barriers, many individuals (especially older individuals) are reluctant to travel from their communities into the “big city” of Pittsburgh and the congested University neighborhood of Oakland, in particular. In addition, investigators rarely have sufficient funds to transport a large portion of their participants from outlying areas. Models of shared transportation, such as University vans or contracts with local transportation companies, will be explored. By coordinating these resources among investigators through the PCIR Core, individual grants will incur fewer costs. If successful, the feasibility of other transportation resources such as purchasing a van for dedicated research use will be explored. Another potential resource would be a *mobile research unit* housed in a vehicle (van, truck, RV) that could take research assessments to participants’ communities. Resources of this type have been used by investigators in the Graduate School of Public Health (L. Kuller and colleagues). However, sharing the cost and benefits among several studies with coordination through the CTSI may offer an efficient model that opens up resources to a wider range of investigators. These programs will be implemented by the CTSI Research Facilitators.

Coordination of clinical cores. As indicated in the Past and Current Clinical and Translational Research Infrastructure Support and Productivity Table B.1 (see Table B.1), the University has numerous clinical research related cores functioning as part of program projects or other center grants, such as the Alzheimer’s Disease Research Center, the Pittsburgh Mind-Body Center, the University of Pittsburgh Cancer Institute, the Pepper Older Americans Independence Center, and the Obesity/ Nutrition Research Center. These cores include functions as diverse as clinical diagnosis, assessment of family members, community outreach, and neuroimaging. Their common feature is expertise in clinical research evaluations. Many of these clinical cores may serve potentially useful functions to CTSI investigators, such as consultation regarding assessment of specific populations, choice of assessments, and management of specialized types of data. Although these clinical cores have been developed with specific grant-related tasks in mind, the expertise offered could greatly benefit CTSI investigators who use PCIR Core resources. Therefore, the PCIR Core will maintain a list of active clinical cores throughout the Schools of the Health Sciences, and, through the CTSI Research Facilitators, will refer investigators to these cores when they might benefit from specific expertise. These clinical cores outside of the CTSI proper will be especially useful resources for junior investigators and pilot studies.

**Specific Aim 2: To coordinate participant and clinical interaction resources by using efficient administrative structures for scientific review, participant safety, resource allocation, and management.** Accomplishing Specific Aim 2 will be the responsibility of individual CTCs, coordinated by

the PCIR Core Director and Administrative Director. While parallel administrative procedures are in place for each of the University-based CTCRCs, these will be reviewed and modified by the PCIR Administrative Coordination Committee to ensure that there is sufficient standardization while also allowing some flexibility for innovation and meeting the specific needs of each type of center. Each center will ensure compliance with Good Clinical Practice (GCP) by following specific guidelines that will be developed, written, and reviewed annually by the PCIR Administrative Coordination Committee. GCP in the context of the PCIR Core refers to ethical and scientific quality standards for the design, conduct, monitoring, recording, analysis, and reporting of patient-oriented research. These standards are designed to assure that data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of participants have been protected. The PCIR Core will be guided by the FDA's regulations on GCP (<http://www.fda.gov/oc/gcp/egulations>), and will collaborate in this effort with the IRB and the Regulatory Knowledge and Support Core of the CTSI. The following paragraphs summarize the research and administrative management procedures of the CTCRCs.

Research protocol recruitment. Promoting the use of the PCIR Core and encouraging recruitment of new protocols is the responsibility of the PCIR Core Director and Administrative Director. New investigators and protocols will be recruited through the CTSI website, printed materials, presentations to investigator groups, and one-on-one discussions with investigators by the PCIR Core Director and CTCRC Program Directors. When an investigator is developing a new research protocol, s/he will contact the appropriate CTCRC Program Director or Administrative Manager to discuss resources and broad administrative and operational requirements, or be referred to the appropriate CTCRC by a CTSI Research Facilitator. The final product of this consultation will be a written research protocol submitted to one of the CTCRCs.

Research protocol review. Conducting a protocol with PCIR resources confers on the CTSI substantial responsibility for ensuring scientific significance, integrity, and protection of human subjects. Meeting these responsibilities is best accomplished by rigorous careful scientific and administrative review. However, several important changes from the current GCRC protocol review procedures are planned. First, research protocols submitted to the PCIR Core will be prepared in the standard University of Pittsburgh IRB format, rather than a separate PCIR format. The PCIR Core submission will also include a description of requested PCIR Core resources. The current GCRC uses an NCCR-recommended protocol format that is similar to the IRB format, but differing slightly in section headings, requirements, and length. This has required investigators to produce two protocol documents, both of which are different from the original PHS 398 application. Thus, while using the IRB protocol format for the PCIR Core may appear to be a small change from current procedures, it will in fact represent a major savings of time and effort for investigators. In the future, when the IRB develops an electronic protocol submission format, the PCIR Core will use that format. The protocol and all consent forms will be submitted to the appropriate CTCRC Scientific Review Committee of the PCIR Core for scientific review prior to IRB review for human subject concerns.

A second major change from the current GCRC system is that different types of protocols will have different levels of scientific review. Thus, for NIH or other federally-approved and funded research grants, PCIR review will focus mainly on implementation issues, and less on the hypotheses or design, which were previously judged meritorious by the sponsor. Pilot studies, foundation-supported studies, and investigator-initiated industry-sponsored studies will receive more rigorous scientific review. Review for multi-site industry-initiated and funded studies, which have very few degrees of freedom in terms of design or methods, will focus on feasibility, safety, and scientific merit to determine whether the study is one that the University should support. Additional review considerations for all submitted protocols will include use of resources, adequacy of funding, and additional considerations or assessments which might enhance the research outcomes.

Review of protocols will be the responsibility of the Scientific Review Committee Chair at each CTCRC site, with the assistance of the Administrative Manager. The review committee at each site will consist of 12-20 investigators with broad expertise in the research areas addressed at that site, in addition to statisticians. Each protocol will receive written review by a minimum of two investigators and a statistician, similar to procedures for the current GCRC. However, a third change from the GCRC review system is that protocols will be assigned, reviewed, and granted expedited approval on a rolling basis, and the Scientific Review Committee will be used for final discussion and approval. Initial reviews will be returned to investigators within two weeks of submission, allowing them to revise and resubmit their protocol quickly. The Committee will discuss the final protocol, and the entire Committee will vote for approval, deferral, or disapproval, and assign a priority score using the NIH 100 – 500 scale. Scores will be used to prioritize resources if access or availability

becomes limited. The Scientific Review Committees will meet at least once per month, depending upon utilization, to review submitted protocols and human subjects concerns. Written agendas and minutes will be kept and submitted to the PCIR Administrative Coordination Committee.

Each protocol supported by the PCIR Core will be required annually to submit a copy of IRB renewal information in order to review recruitment, use of resources, and productivity in terms of publications. Protocols with recruitment less than 50% of the anticipated target will be required to submit a letter of explanation to the Scientific Review Committee indicating reasons for low recruitment and plans for remediation. The Committee will have three options: suspend the protocol; allow continued recruitment; or allow recruitment with stipulations for more frequent reporting on progress. The Committee will also offer suggestions on additional CTSI resources to help improve recruitment. In addition, any unresolved human subjects concerns will lead to temporary or permanent suspension of the protocol. Any IRB modifications for a protocol will be submitted simultaneously to the appropriate CTRC for review.

Research protocol implementation. Following scientific review and approval, investigators and their research team will meet in person with administrative and clinical staff at the CTRC to begin implementation of the protocol. Implementation will include a set of written orders individualized for each subject; clear description of research procedures, including a written manual of operations when necessary; and lines of reporting for possible difficulties with research assessments. Mechanisms for data collection, data entry, and data management (including resources of the CCTI) are a required component of implementation; if adequate mechanisms are not in place, conduct of the protocol will be deferred until this is accomplished. Clear lines of responsibility must be established for protocol staff and CTRC staff. Implementation also involves assessment of required resources and allocating costs and cost-recovery mechanisms, as described below.

Conduct of research protocol. Conducting the protocol requires scheduling subjects for appointments, a joint activity by the specific protocol staff and CTRC staff. At the designated time of the research visit, CTRC staff will assume responsibility for conducting research procedures, supplemented as previously arranged by protocol-specific staff. The PCIR Core is committed to following applicable federal policies and regulations regarding protocol conduct (e.g., <http://www.fda.gov/gcp/regulations>).

Protection of human subjects. Given the responsibility that the CTSI assumes for research subjects being studied in its facilities, protection of human subjects is a high priority. Human subject protection will receive specific focus at three stages. First, human subject concerns will be a routine component of the scientific review process within the CTSI. Second, all protocols will undergo a second review specifically focusing on protection of human subjects at the IRB. Third, all staff in the CTRCs are required to successfully complete the University's on-line human subject research education module. In addition, the CTSI Research Education, Training, and Career Development Core will have a role in the education of both CTRC and research staff. Identification of issues regarding subject safety is the responsibility of all research staff. If such concerns arise during the course of a study using the PCIR Core, staff will report their concern both to the study investigator and to the Program Director of the CTRC in question, who will follow up with the investigator and, if necessary, with the IRB. All PCIR Core staff will be expected to follow federal, Commonwealth of Pennsylvania, University of Pittsburgh, and UPMC reporting requirements regarding adverse events, protocol deviations, incidents, and serious events.

The PCIR Core will use the Research Participant Advocate (RPA) system [known as Research Subject Advocate (RSA) as developed under the existing GCRC structure], but with modifications to make optimal use of this valuable system. The primary responsibility of these RPAs will be to protect human subjects by assisting with protocol and consent form development, ensuring accuracy of consent forms, ensuring appropriateness of Data Safety Monitoring Plans, assisting with monitoring and reporting plans of adverse events, and reviewing proposals to ensure that study procedures are accurately translated into appropriate research patient protocols. This support will be made available to CTSI investigators who are using the CTRCs, junior investigators, students, and others (as requested or identified). Additional details regarding the RPA role in the CTSI are included in the Regulatory Knowledge and Support Core section of this application.

Fiscal management. Day-to-day fiscal administration will be the responsibility of the PCIR Financial Administrator in conjunction with the Administrative Managers and Program Directors, with oversight and integration from the PCIR Core Director and Administrative Director. The Financial Administrator will



supervise a Fiscal Assistant, and will report independently to the CTSI Financial Administrator, Kathy Sidorovich. Working budgets will be prepared annually in conjunction with the overall CTSI.

In virtually every case, actual costs for conducting a research study are shared between the CTRC, the individual research grant, and the sponsoring institutions. The exact apportioning of costs for each protocol will be determined during the recruitment and implementation stages, prior to the conduct of the research study. In general, costs covered by the PCIR Core include personnel, routine supplies, equipment, information and data management, administration, and space; costs covered by the research study include protocol-specific outcome measures, laboratory assay costs, and protocol-specific personnel. The CTSI and research studies, however, cannot cover all the costs of running the individual CTRCs. The sponsoring institutions—The

University of Pittsburgh Schools of the Health Sciences, specific Departments, and UPMC—play crucial roles in cost-sharing for this enterprise. One of the responsibilities of the CTSI administration is to negotiate cost-sharing between the CTSI and the sponsoring institutions. Table 4 summarizes the general approach to cost sharing in the PCIR Core.

Table 4: Cost Sharing in the PCIR Core

Entity	Individual Research Protocol	PCIR Core	Sponsoring Institutions (University of Pittsburgh, UPMC)
Fiscal responsibility	<ul style="list-style-type: none"> <li>•Screening laboratory studies</li> <li>•Assay costs for outcome measures</li> <li>•Specific personnel for specialized procedures</li> <li>•Protocol-specific supplies and equipment</li> </ul>	<ul style="list-style-type: none"> <li>•Research facility costs (rent, hourly research rate)</li> <li>•Research staff (nurses, techicians)</li> <li>•Routine supplies and equipment</li> <li>•Shared major equipment</li> </ul>	<ul style="list-style-type: none"> <li>•Shared research facility costs</li> <li>•Infrastructure costs</li> <li>•Major equipment (capital costs)</li> <li>•Research rates charged to PCIR investigators</li> </ul>

Current GCRC funding mechanisms correlate poorly with the intensity and actual usage of resources; many outpatient studies make intense demands on nursing and other resources, and some inpatient studies simply require an overnight stay with little intervention. Therefore, with the transformation from GCRC to CTSI, a change in cost accounting to a system based on the time and intensity of research visits rather than their characterization as inpatient or outpatient will be instituted. The time required for a research visit is estimated in a fairly straightforward fashion, and modified based on actual experience. The intensity of research visits will be defined by the time-utilization of a single nurse/technician. By estimating the time and intensity of visits for each approved research protocol and the number of visits anticipated, total staffing requirements and mechanisms for cost-sharing with individual research studies can be estimated.

Industry-initiated studies will be responsible for covering all costs associated with research studies, including costs for staff, supplies, and fees to cover infrastructure and equipment costs. These costs will be standardized across industry-initiated studies at each CTRC site. In the current GCRC, industry-initiated studies account for approximately 24% of all research protocols, 8% of bed-days, and 10% of outpatient research visits. Cost recovery from industry-initiated studies will be the responsibility of UPMC, and will be budget-neutral from the perspective of the PCIR Core.

### **Specific Aim 3: To develop additional resources for participant and clinical interactions through collaboration with the CTSI Center for Clinical and Translational Informatics (CCTI).**

The PCIR Core will provide a platform for informatics innovation in three key areas: Research data management, scientific review, and research administration. The ultimate goals are to ensure adequate and appropriate informatics support wherever a study is conducted, and to ensure that the best information technology tools are available to the widest range of investigators while avoiding duplication in development and implementation. The PCIR Core will provide resources that are particularly valuable to the clinical and translational research activities of junior faculty and trainees enrolled in CTSI training programs.

Informatics innovation and interaction. The PCIR will work with the CCTI on developing informatics resources within the CTSI. Existing, productive collaborations between the Information Technology and Biostatistics Core of the Adult GCRC and the Department of Biomedical Informatics will greatly facilitate the development of these resources. . Three specific areas have been targeted for further informatics development: research data management, scientific review, and research administration.

- Establishing a straightforward and customizable *data management system* for investigators—particularly junior investigators who have few resources at their disposal—is a priority within the PCIR Core. The major application being developed within the CCTI is the Clinical Trials Management Application (CTMA), which has been endorsed by the UPMC Clinical Trials Office and the University of Pittsburgh, Office of Clinical Research (see CCTI for further details). The overall goal of the CTMA is to create a secure, web-based,

integrated application to support the clinical and administrative functions of the clinical trials process. CTMA provides functionality in the following features sets: 1) Administrative and regulatory management; 2) Clinical research data management, 3) Study parameter management (e.g., adverse event and protocol event tracking); and 4) Flexible reporting tools for research reports. These functions have a wide range of features such as patient screening/registration, IRB approvals, submission and renewals, patient treatment schedule, adverse events and clinical data collections for fiscal-based reporting. In addition to CTMA, existing tools and functions from the GCRC program will be integrated, such as electronic form development, relational data base advice, and security and back up services. The CCTI team has also developed the use of on-line analytical processing (OLAP) data mining capabilities that are of particular value in translational research. This resource is synergistic with the data warehouse that CTMA also feeds, allowing data collected from clinical therapeutics trial management to be coordinately mined with data collected from translational research endeavors.

- Management of the *research review* process through improved informatics offers substantial advantages of efficiency for both investigators and reviewers. Although this application may appear mundane, it will save time and effort, thereby making use of the PCIR Core more attractive to new CTSI investigators. Building on a system developed within the Adult GCRC, submitted protocols will be posted on-line, where investigators and reviewers will have secure access. Review forms for all of the Scientific Review Committees will also be posted online. Reviewers will use these forms to post their review, and investigators can both access and respond to these reviews in the same way. The website will also indicate the current status of each protocol, whether under review, approved, ongoing, etc. Finally, the website will be used to post annual renewal information for review by CTMC administrative staff and leadership.
- Several tools for *research and clinical administration* will benefit from continued informatics development, including systems for research subject scheduling, tracking of research visits (by protocol, by investigator, by date), and fiscal management. Through improved tracking of utilization and costs, more efficient research administration mechanisms can be developed. This work will build on tools that have been developed within the GCRC, but will be expanded to all of the PCIR Core sites. Specifically, the Protocol Data Management System has been used routinely by nursing staff, nursing coordinators, and investigators at the MUH GCRC. This system is linked to the CTMA-Enterprise Scheduling System, a web-based Cold Fusion application designed to manage patient and resource scheduling for clinical research. The application includes components for managing participant information (e.g., demographics, protocols), administrative functions (e.g., participant check-in, daily notes, staffing information), supply preparation worksheets, and virtual bedboards. The system also links to a web-based reporting module.

**Specific Aim 4: To provide resources to support the research activities of junior faculty and trainees enrolled in CTSI training programs.** The PCIR Core will provide valuable resources for trainees involved in the various CTSI education programs. For instance, junior investigators enrolled in the current K12, K30, and T32 programs will often need the facilities and staff of the PCIR Core to conduct pilot and feasibility studies. In addition to the obvious benefits of having resources to conduct their studies, junior investigators will enhance their education through the process of protocol review, implementation, and conduct in a supportive environment. Trainees will also have the opportunity to audit CTMC Scientific Review Committee meetings in order to learn more about how scientific review is typically conducted. Information on PCIR Core resources will be provided to trainees via web site, talks given to trainee groups, and discussion with CTSI Research Facilitators. The Pilot and Collaborative Translational and Clinical Studies Core will also interact with the PCIR Core around the conduct of new studies, providing another opportunity to support the educational mission of the CTSI.

**Specific Aim 5: As part of the CTSI Tracking and Evaluation Plan, to develop a process for evaluating the PCIR Core.** This is a significant initiative that will lead to transformation in the PCIR; no similar process of evaluation currently exists. This initiative is discussed in detail in the Tracking and Evaluation Plan of the CTSI. Accomplishing Specific Aim 5 will be the responsibility of the PCIR Core as a whole, under the leadership of the Core Director, in collaboration with Dr. Rubio, who leads the Tracking and Evaluation Plan of the CTSI. Briefly, two major types of evaluation activities will be conducted: 1) Evaluating the changing needs of the clinical and translational research communities with respect to participant and clinical interaction resources. This type of evaluation will include surveying the needs of current PCIR Core investigators and investigators not currently using the PCIR Core, and getting regular feedback from CTMC

Directors and staff. 2) Evaluating the effectiveness of the PCIR Core both qualitatively and quantitatively. Results of the evaluation process will be reviewed on an annual basis by the PCIR Administrative Coordination Committee, and will be used for strategic planning in the PCIR Core. Results of the annual evaluation process will also be brought to the CTSI Executive Committee for comment and input. During the evaluation process, the entire range of clinical and translational investigators (trainees to professors) from a broad range of home disciplines, departments, and schools will be surveyed.

**Proposed timeline.** Since the PCIR Core represents a transformation of existing resources in the GCRCs at the University of Pittsburgh, it will have fairly aggressive timeline. The University-based CTCRCs are already operational, although they will continue to undergo administrative and operational transformations under the CTSI mechanism. Changes are expected to be completed by the end of Year 01. The Community CTCRC does not yet formally exist, and will require a longer timeline to become fully functional. During Year 01, fiscal and administrative relationships with community sites will be investigated, so that initial research studies can be conducted at UPMC Braddock Hospital in Year 02. Implementation of studies at other components of the Community CTCRC is targeted for Year 03. The development of translational informatics systems will be an ongoing process. However, all administrative aspects of the informatics system are expected to be operational by the end of Year 01 at each CTCRC site, and a functional data management system available for investigator use by the end of Year 03. The evaluation and education component of the PCIR Core will be implemented in Year 01. In summary, Year 01 will be a year of transition from the current GCRC system into the CTSI, and all major functions and structures will be in place and operational by the end of Year 03.

**CTSI relationships.** The PCIR Core will interact with other Cores and functions within the CTSI to transform clinical and translational research at the University of Pittsburgh. Table 5 summarizes how this Core will interact with other CTSI components toward this end.

### **Summary of the Participant and Clinical Interaction Resources Core.**

The PCIR Core provides facility and staffing resources to support clinical and translational research. The PCIR Core grows out of a strong and productive GCRC tradition at the University of Pittsburgh. With the development of the CTSI, the GCRC system will be transformed in several major ways. These include a transition toward community-based participant and clinical interaction resources; greater specialization of existing PCIR resources; substantially streamlining the research review and administrative processes; developing stronger interactions with informatics and educational components of the CTSI; and developing a process of ongoing quantitative and qualitative review to determine the optimal utilization patterns for PCIR.

### **Literature Cited:**

1. Goodpaster BH, Stenger VA, Boada F, McKolanis T, Davis D, Ross R, Kelley DE. Skeletal muscle lipid concentration quantified by magnetic resonance imaging. *Am J Clin Nutr.* 2004;79:748-754.
2. Menshikova EV, Ritov VB, Toledo FG, Ferrell RE, Goodpaster BH, Kelley DE. Effects of weight loss and physical activity on skeletal muscle mitochondrial function in obesity. *Am J Physiol Endocrinol Metab.* 2005;288:E818-E825.
3. Heine RP, Ness RB, Roberts JM. Seroprevalence of antibodies to Chlamydia pneumoniae in women with preeclampsia. *Obstet Gynecol.* 2003;101:221-226.

Table 5: PCIR Core Relationships with other CTSI Cores and Functions

CTSI Component	Interactions with PCIR Core
Development of Novel Clinical and Translational Methodologies	•PCIR Core will provide research sites for application of novel methodologies
Pilot and Collaborative Translational and Clinical Studies	•PCIR Core will provide research sites for conducting pilot studies •PCIR will support informatics needs of pilot studies
Center for Clinical and Translational Informatics	•Informatics Core will work with PCIR Core to develop applications for data management, protocol review, fiscal and operational administration
Design, Biostatistics, and Clinical Research Ethics	•Protocol review by PCIR Scientific Review Committees will include review of human subjects issues and consultation as necessary with this core
Regulatory Knowledge and Support	•Protocol review by PCIR Scientific Review Committees will include review of human subjects issues and consultation as necessary with this core
Community PARTners	•Community CTCRC will benefit from knowledge and relationships established by Community PARTners Program •Community CTCRC will provide research education, opportunities, and ongoing presence in communities
Translational Technologies and Resources	•PCIR Core will study research participants whose biological samples are assayed by operational cores
Research Education, Training, and Career Development	•PCIR Core will provide clinical resource for trainees conducting pilot or feasibility studies •PCIR Scientific Review Committees will provide opportunity for trainees to audit research review process
Rapid Commercialization	•PCIR Core can provide research sites for testing of new devices/equipment/treatments with commercialization potential
Tracking and Evaluation Plan	•PCIR has collaboratively developed a quantitative and qualitative evaluation strategy

4. Hubel CA, Bodnar LM, Many A, Harger G, Ness RB, Roberts JM. Nonglycosylated ferritin predominates in the circulation of women with preeclampsia but not intrauterine growth restriction. *Clin Chem*. 2004;50:948-951.
5. Lain KY, Wilson JW, Crombleholme WR, Ness RB, Roberts JM. Smoking during pregnancy is associated with alterations in markers of endothelial function. *Am J Obstet Gynecol*. 2003;189:1196-1201.
6. Germain A, Nofzinger EA, Kupfer DJ, Buysse DJ. Neurobiology of non-REM sleep in depression: Further evidence for hypofrontality and thalamic dysregulation. *Am J Psychiatry*. 2004;161:1856-1863.
7. Nofzinger EA, Buysse DJ, Germain A, Price JC, Meltzer CC, Miewald JM, Kupfer DJ. Alterations in regional cerebral glucose metabolism across waking and non-rapid eye movement sleep in depression. *Arch Gen Psychiatry*. 2005;62:387-396.
8. Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. *Am J Psychiatry*. 2004;161:2126-2131.
9. Arslanian SA, Bacha F, Saad R, Gungor N. Family history of type 2 diabetes is associated with decreased insulin sensitivity and an impaired balance between insulin sensitivity and insulin secretion in white youth. *Diabetes Care*. 2005;28:115-119.
10. Arslanian SA, Lewy VD, Danadian K. Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and beta-cell dysfunction and risk of cardiovascular disease. *J Clin Endocrinol Metab*. 2001;86:66-71.
11. Berger RP, Dulani T, Adelson PD, Leventhal JM, Richichi R, Kochanek PM. Identification of inflicted traumatic brain injury in well-appearing infants using serum and cerebrospinal markers: a possible screening tool. *Pediatrics*. 2006;117:325-332.
12. Bruce ML, Ten Have TR, Reynolds CF, Katz IR, Schulberg HC, Mulsant BH, Brown GK, McAvay GJ, Pearson JL, Alexopoulos GS. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: A randomized controlled trial. *JAMA*. 2004;291:1081-1090.
13. Reynolds CF, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, Houck PR, Mazumdar S, Butters M, Stack JA, Schlernitzauer MA, Whyte E, Gildengers A, Karp J, Lenze E, Szanto K, Bensasi S, Kupfer DJ. Maintenance treatment of major depression in old age. *N Engl J Med*. 2006;354:1130-1138.
14. Bauer DC, Garnero P, Bilezikian JP, Greenspan SL, Ensrud KE, Rosen CJ, Palermo L, Black DM. Short-term Changes in Bone Turnover Markers and Bone Mineral Density Response to Parathyroid Hormone in Postmenopausal Women with Osteoporosis. *J Clin Endocrinol Metab*. 2006.

*Transformation of Research*  
**Translational Technologies and Resources**

The University of Pittsburgh and the UPMC hospitals are home to myriad research centers, institutes, core laboratories, and clinics that support research in the broad arena known as the health sciences. Among these are several core facilities that support translational research, where “core facility” is used to denote a service facility that has state of the art equipment, trained technical staff to support the use of the equipment, consulting services, and educational resources. These cores may be operated as fee-for-service entities, as collaborative resources, or some combination thereof; in any case, the services provided are widely available to investigators from across the health sciences and, in many case, from across the University campus. There is generally no restriction on the area of biomedical research to which core services may be applied. However, there are other organized activities on campus that serve as more localized cores, supporting a select group of investigators, often within a specified area of research. The aims of Translational Technologies and Resources Core (TTRC) activities with the University of Pittsburgh Clinical and Translational Research Institute are:

1. To establish mechanisms for assessing the translational resource needs of the CTSI research community and, in response, provide broadly needed resources by developing new core facilities that have the tools, educational programs, and expertise to allow integration of new technologies into translational research and clinical research and practice. *When appropriate, build cores that derive from methodologies/technologies developed under the “Novel Clinical and Translational Methodologies Core.”*
2. As appropriate, to develop a network of interaction between localized cores that are focused on similar services/disciplines to minimize duplication, enhance efficiency, and broaden access.
3. To develop robust mechanisms for informing the CTSI membership about core services that are available, with a focus on educating the CTSI research facilitators so as to enhance their effectiveness in referring investigators to available research resources.

## **BACKGROUND**

### **Existing Translational Technologies and Resources.**

If one takes a liberal approach to defining and counting the research cores within the University of Pittsburgh Academic Health Center, there are at least 300 such entities. This is misleading, however, since one *core facility* may provide the “core” for multiple research units. For example, the Transgenic and Chimeric Mouse Facility is a named “core” in the University of Pittsburgh Cancer Institute’s Cancer Center Support P30 grant and is also a named “core” in several other “P” mechanism awards. Alternatively, some “cores” are directly tied to the research program supported by a given grant; they are intended to support the research of a small cadre of investigators and they are, in general, not available to the broader research community. That they are not broadly accessible does not diminish their value to the translational research enterprise; they exist because of the valuable services that they do provide. Table B provides an overview of the extensive set of “cores” and “core facilities” available to University of Pittsburgh health sciences investigators.

While there is no agreed upon definition of a *core facility*, it is informative to look at the descriptions of *core facilities* in the NIH intramural program.

- The “NIEHS Division of Intramural Research Core Facilities,” described at <http://dir.niehs.nih.gov/corefac.htm>, share the common theme that they provide services, access to technology, consultation, and training.
- The NIDDK Intramural Research program established a Microarray Core Facility “to provide microarray services for investigators in the institute, by establishing a cost recovery unit whose instruments are operated by its staff members” ([http://intramural.niddk.nih.gov/research/labbranch.asp?Org\\_ID=571](http://intramural.niddk.nih.gov/research/labbranch.asp?Org_ID=571)).
- NIMH and NINDS support the functional MRI Facility (FMRIF), “a core resource serving the intramural research program ... the Facility provides a complete environment for stimulus presentation, monitoring and recording subject behavior and physiology while performing functional MRI. Additional services include providing for temporary data storage, data transfer, instruction on running the scanner, as well as assistance, during working hours, in performing fMRI ... FMRIF currently has a total of 9 full time scientists and staff who provide services including scanner operation and instruction, subject interface device development and maintenance, data transfer and storage infrastructure, and multiple web-based services” (<http://intramural.nimh.nih.gov/fmri/>).

- NIAMS has a core X-ray crystallography facility. “The purpose of the X-ray crystallography core facility is to provide equipment, training, assistance, and technological innovations for determining three-dimensional structures of protein and other macromolecules.” Services provided by the facility include crystallization, X-ray characterization of crystals, data collection, processing and quality analysis of data, structure determination, molecular modeling, molecular docking and structure visualization and analysis ([http://www.niams.nih.gov/rtbc/labs\\_branches/ost/xray/](http://www.niams.nih.gov/rtbc/labs_branches/ost/xray/)).

The common thread in the description of these facilities is that each is a service facility that has state of the art equipment, trained technical staff to support the use of the equipment, consulting services, and educational resources. It is this concept for a *core facility* that is used here.

Much of scientific discovery has been driven by a parallel process of building on knowledge and of developing new research technologies that allow for new modes of inquiry. Cellular and organism imaging, cell sorting, Genomics, Proteomics, system modeling, transgenic methods, and other technologies have all transformed and broadened the translational research enterprise. With the development of these technologies has come a need for technical expertise and for the ability to manage, analyze, and interpret exponentially expanding datasets. For much of basic research, there is a predictable cycle in the development and maturation of a research methodology and also in its eventual maturation into a tool that can be translated into clinical research and eventually incorporated into clinical practice.

Technological advances are frequently initiated by the efforts of a single investigator or a small team of scientists. Once proof of concept of a new technology has been established and published, then its potential applications to other areas of research are rapidly recognized by the broader scientific community. Typically, it is a small group of researchers with vested interest in an emerging technology who promote its development and application. Gradually the awareness and applicability of the technology expands to a broader group of scientists. Frequently at this stage, industry will attempt to create a kit or standardize the technology in a fashion that is potentially marketable. If the cost and level of required expertise are relatively low, then the methodology may be directly exported to individual laboratories. However, if the cost of the technology is high and/or the technical expertise required to use the technology is high, then it is usually more efficient and more cost effective to develop a core facility that provides the critical level of expertise and support that is needed to bring the technology to bear on a broad spectrum of research activities. In some cases, as discussed below, aspects of the technology mature to the point that costs decrease and it is reasonable to export the technology from the core to the laboratory of an individual investigator or to a common laboratory that serves a small group of investigators. There are also instances in which it becomes cost-effective for a for-profit company to sell “services” using a mature technology to academic investigators; the large, collective volume of activity that a company can maintain leads to increased efficiency and hence a lowering of costs per given service. In such cases, core facilities developed at academic institutions must be competitive with commercial vendors, or they will close. Traditionally, this results in increased access to the technology for the scientific community and greater flexibility in providing services and consultation. Investigators and core facility personnel must continuously evaluate the advantages and disadvantages of using and maintaining a local facility versus outsourcing to a commercial laboratory. Ultimately, the core technology may be outmoded by newer methods in which case the cycle begins again with the next generation of technology. This cycle of research technology development has many variations but, in recent years, the capacity of newer technologies to handle very large numbers of samples and to generate vast amounts of data has created a greater need for centralized institutional technology resource management and higher levels of technical and informatics support.

#### Core Facilities at the University of Pittsburgh Academic Health Center

Translational Technologies and Resources comprise the basic research methodologies and core facilities that are of critical value to translational and, in some cases, clinical research. Samples interrogated in these facilities – subcellular, cellular, tissue, organ – may be derived from model organism systems, ranging from bacteria or viruses to animal models, or from human specimens.

The primary biomedical core facilities, as defined above, that support basic and translational research and that are available to investigators in the University of Pittsburgh Academic Health Center are described in summary below. As noted previously, there are many other cores that support a more limited number or spectrum of investigators than do these core facilities. While many of the core facilities are available to investigators under fee-for-service arrangements, at least in part, others support research through collaborative activities or through core funding provided by institutional or grant resources.

- The Biomedical Research Support Facility is a group of specialty core facilities: (a) The Biosensor Facility provides real-time biomolecular interaction analysis utilizing a Biacore 3000 system; (b) The DNA Sequencing Core performs sequencing reactions on submitted DNA templates and primers, analyzes the products by capillary electrophoresis on automated sequencers, and provides the resultant sequences as an electronic database. In addition, the core personnel consult with investigators in the preparation of DNA for automated sequencing and assist with DNA sequence data analysis; (c) The Mass Spectrometry Core operates a triple quadrupole mass spectrometer and a matrix assisted laser desorption ionization time-of-flight mass spectrometer for high sensitivity analysis of proteins, peptides, lipids and small molecules by electrospray ionization in either the positive or negative ion mode; (d) The Peptide Synthesis core provides comprehensive services for synthesis, purification, and characterization of synthetic peptides. Peptides may also be prepared with specialized modification, such as acetylation, biotinylation, phosphorylation, cyclization, or fluorescent dyes; (e) The Structural Biology Facility provides Circular Dichroism and UV-VIS spectral measurements for determination secondary structure elements of proteins.
- The Center for Biologic Imaging provides centralized imaging services including light fluorescent microscopy, confocal laser scanning, electron microscopy, advanced computer aided morphometry, and image analysis.
- The Division of Laboratory Animal Resources provides the animal husbandry and veterinary services for the health science community's animal research program. The division educates, trains, and informs the University biomedical community, as well as the public, regarding laboratory animal science. The programs and facilities are USDA registered and covered under an Assurance with the Office of Lab Animal Welfare (OLAW) of the PHS and accredited by the American Association for the Assessment and Accreditation of Lab Animal Care (AAALAC), within the Division.
- The Functional Imaging Research Program (FIRP), a joint facility of the University of Pittsburgh and UPMC, provides investigators with use of two powerful imaging modalities, positron emission tomography (PET) and magnetic resonance (MR) imaging. The Magnetic Resonance Research Center is dedicated to the development and application of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) for medical and biological research and is forging new paths in the use of functional MRI to study cognitive, sensory, and motor function in the brain. The Positron Emission Tomography (PET) Facility supports a variety of research efforts in collaboration with faculty in the Departments of Psychiatry, Neurology, Radiology, Medicine, and Anesthesiology and the University of Pittsburgh Cancer Institute.
- The Genomics and Proteomics Core Laboratories foster the implementation of modern Genomics and Proteomics in research, education, and clinical care encompassed by the University of Pittsburgh Schools of the Health Sciences. The Laboratories are equipped with state-of-the-art instrumentation and provide a variety of standard as well as customized Genomic and Proteomic analyses to university researchers and their collaborators. Genomics services include DNA sequencing, candidate gene and whole genome SNP genotyping, RNA/DNA extraction, purification and QC services, Affymetrix and Illumina gene expression micro-arrays and TaqMan® real-time PCR. Proteomics services offered include Protein Identification by Peptide Mass Fingerprinting, de novo sequencing, PTM analysis, DiGE and standard 2D PAGE and LC MALDI. The Proteomic platforms available include a high performance MALDI TOF-TOF MS/MS, MDLC MS<sup>n</sup> ion trap and a basic MALDI MS. A 12 Tesla FT-MS will be available in mid-year 2006. (See below for details and for definitions of the acronyms used in this summary description.)
- The John A. Swanson Micro and Nanotechnology Lab, established by the School of Engineering, houses a strong research team with expertise in the areas of microfabrication, smart materials (piezoelectric and electrostrictive materials, magnetostrictive materials and shape memory alloys), functional polymers and devices, micro power generation systems, and MEMS device design and applications. The facilities are available for University-wide Microelectromechanical Systems (MEMS) and Nanotechnology research and education activities. The current facilities can be utilized for the fabrication, packaging, and testing of various thin and thick film materials, microsensors and microactuators, and various functional materials based micro- and nano-scale devices and structures.
- The Pittsburgh NMR Center for Biomedical Research, located at Carnegie Mellon University (CMU) and jointly supported by CMU and the University of Pittsburgh, brings together scientists and clinical investigators in a concerted research program focusing on the application of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) to the biomedical sciences. Center investigators from Carnegie Mellon University, the University of Pittsburgh and local hospitals use animal and cellular models

in their studies and have expertise in such diverse fields as biology, physics, computer science, neuroscience, medicine, and surgery.

- The Pittsburgh Supercomputing Center, a joint effort between the University of Pittsburgh, Carnegie Mellon University, and Westinghouse Electric Company, provides university, government, and industrial researchers with access to several of the most powerful systems for high-performance computing, communications and data-handling available to scientists and engineers nationwide for unclassified research. As a leading partner in the TeraGrid, the National Science Foundation's program to provide a coordinated national cyberinfrastructure for education and research, PSC works with other TeraGrid partners to harness the full range of information technologies to enable discovery in U.S. science and engineering.
- The Transgenic and Chimeric Mouse Facility provides a centralized service to produce transgenic and chimeric mice for investigators throughout the University of Pittsburgh and its affiliated institutions and hospitals. Services include DNA Microinjection, Mouse ES Cell Electroporation, Mouse ES Cell Microinjection, Embryo Derivation, Cryopreservation of embryos and derivation of ES cell lines from blastocysts.
- The Benedum Oncology Informatics Center and the Center for Pathology Informatics together form a cluster of tightly interrelated core resources, including Clinical Trials Informatics Services, the De-ID Broker Services, and Analytical Services. The Center for Clinical and Translational Informatics proposed under the CTSI is an expansion of these resources.

Specific Aim (1) of the TTRC addresses the need for additional core facilities that will support the research enterprise at the University of Pittsburgh Academic Health Center.

### **An Example of the Evolution of a Translational Core Resource.**

#### The Genomics and Proteomics Core Laboratory

The University of Pittsburgh Genomics and Proteomics Core Laboratories provide an illustrative example of the development and evolution of translational research cores at the University of Pittsburgh Academic Health Center. While the Genomics and Proteomics capabilities are distinct from each other, and hence there are two scientifically distinct laboratories, they are managed by a single administrative unit. The GPCL offer expert knowledge and support with experimental design, protocol development, technical support, data analysis, and interpretation; core leaders and technicians are available to provide the necessary guidance and support through direct consultation.

The Genomics Core Laboratory came into being in 1996 as the Center for Genomic Sciences, a resource developed by, and for, a small group of investigators in the Division of Gastroenterology, Hepatology and Nutrition of the Department of Medicine (School of Medicine). In 1998, the primary platform in use for differential gene expression analysis was the Genehunter<sup>®</sup> differential display method with validation using RNase protection assays. DNA sequencing was performed on 36 lane slab gels and genotypes were hand-recorded; a genome wide scan required over one year for the analysis of a family of 48 subjects. With the agreement of the Center for Genomic Sciences leadership, the Genomics Core Laboratory (GCL) was established in 1999 by the Senior Vice Chancellor for the Health Sciences, shortly after he arrived at the University. It was established in recognition that a limited number of Genomics technologies such as DNA sequencing and microsatellite genotyping had become sufficiently robust that an increasingly broad range of biomedical investigators wanted to incorporate data from these technologies into their research studies. Establishment of the core enabled investigators to utilize a highly organized quality controlled (QC) and quality assured service for processes such as DNA extraction where QC and sample integrity were of a more fundamental issue than was the capability of the technology. The availability of robust quality control continues to be a major factor in the decision by investigators to use Core services, especially for clinical studies. The Core also developed expertise in RNA extraction from many tissues, using a variety of techniques.

In the period between 1999 and 2001, I.M.A.G.E. Consortium (LLNL) cDNA clones were added as a resource along with equipment for custom microarray printing and scanning for differential gene expression analysis. The microarray equipment was initially placed in the laboratory of an investigator with expertise and vested interest in microarray studies, and this investigator served as a resource for the Genomics Core. Two years later, the microarray equipment was incorporated into the Core. TaqMan<sup>®</sup> real time PCR was added as a functionality for result validation with the purchase of an ABI Prism 7700<sup>®</sup> Sequence Detection System. This



system was initially purchased for a specific investigator who was expert in this technology. He subsequently trained multiple investigators and technicians and eventually relocated the equipment to the Core to allow for campus wide usage. At the time, these technologies were considered to be cutting edge, and, because of cost and lack of resident expertise, they would have been out of reach to most investigators were the Core not available. It became clear that projects requiring significant sequencing were being affected by the turnaround time and the costs associated with slab gel sequencing and genotyping. Therefore, in 2001, an ABI Prism 3700<sup>®</sup>, 96 capillary DNA analyzer was purchased in order to increase DNA sequencing and genotyping throughput and to lower the cost for each. During this time single nucleotide polymorphisms (SNPs) were being recognized as a valuable tool for genotyping, and SNP genotyping was added as an application utilizing the ABI Prism 7700<sup>®</sup>.

In 2001, the Proteomics Core was launched with the purchase of a Ciphergen ProteinChip<sup>®</sup> chip reader that was requested by campus investigators because of reported successes in utilizing this technology to define protein and peptide signatures that provided diagnostic capabilities for cancer phenotypes. It seemed apparent that successes in the cancer forum could translate to similar successes for other disease types. The Senior Vice Chancellor for the Health Sciences agreed to provide funds necessary to bridge the gap between the purchase price and the financial commitments from departments within the six schools of the health sciences to allow for this purchase. In the first two years of use of the Ciphergen system, the UPCI invested in robotics that made the data acquired by this system more reproducible. Also during this time, the Senior Vice Chancellor invested in state-of-the-art analytical mass spectrometers for the Proteomics Core within the GPCL. It became apparent that the transfer of the Ciphergen system to the UPCI was appropriate, under the agreement that all investigators who requested time on the system would maintain access to it.

In 2002, additional Core Proteomics capabilities became available with the purchase of 2D PAGE (two dimensional polyacrylamide gel electrophoresis) equipment and the hiring of expert technical staff. In early 2003, an LC ESI ion trap MS (liquid chromatography, electrospray ionization ion trap mass spectrometer) and a tandem MALDI TOF-TOF (matrix assisted laser desorption ionization time-of-flight time-of-flight) mass spectrometer were purchased. The development and funding of this Core, provided by the Senior Vice Chancellor for the Health Sciences, was in response to increasing request by university researchers driven by proteomic based questions and the increased onus for mechanistic proof placed on investigators by grant application and manuscript reviewers.

Also in 2002, an Affymetrix Scanner and Fluidics station was purchased to allow the GeneChip<sup>®</sup> technologies to be performed. The demand for this service increased due to a reduction in system and chip costs and the publication of manuscripts utilizing this platform in clinical research. This service was transitioned from the laboratory of an individual investigator into the Core in order allow for economies in technical personnel and administration.

In 2003, the ABI Prism 7900 HT<sup>®</sup> Sequence Detection System (TaqMan<sup>®</sup>) was purchased in order to allow for higher throughput SNP genotyping in 384 well plates. An ABI Prism 3730<sup>®</sup> DNA analyzer was also purchased at this time to replace the outmoded ABI Prism 3700<sup>®</sup> analyzer and reduce sequencing costs further. In 2004, the Affymetrix GeneChip<sup>®</sup> scanner was replaced with the new model to allow for higher resolution scanning of the new generation of GeneChip<sup>®</sup> including expression arrays, SNP chips, resequencing arrays, and others. The advent of Affymetrix GeneChip Mapping 10K<sup>®</sup> whole genome SNP chips replaced the more arduous and uncertain art of microsatellite genotyping with a more accurate, higher density, and higher throughput whole genome gene mapping technology. In 2004, an Illumina<sup>®</sup> Beadstation 500GX was acquired to allow for high throughput custom SNP genotyping gene association studies. This enabling technology was required to allow investigators to study multiple candidate genes for disease phenotypes in a cost effective manner. This platform allows for the simultaneous measurement of up to 24,000 investigator selected SNP loci and over 500,000 loci on a single fixed content mapping chip.

In 2005, the Proteomics Core added a walkup, investigator-friendly MALDI TOF MS and a nano MDLC (multi-dimensional liquid chromatograph) connected in tandem with a Probot<sup>®</sup> MALDI target spotting instrument to allow for the study of complex mixtures and low abundance analytes. When coupled with quantitative techniques, this technique also allows for high information content quantitative profiling of multiple samples. The GPCL implemented a core-wide Laboratory Information Management System (LIMS) to allow for integrated sample tracking for Genomics and Proteomics within the same system and is creating specifications for the next phase implementation of a billing system to be integrated into this LIMS. As noted, the Proteomics Core will be adding a 12 Tesla Fourier Transform MS in 2006.

The GPCL were conceived and developed in order to provide technical services in the most cost effective timely manner while providing for the highest quality of data. Service offerings are developed according to need where the most common reasons for using the facility are equipment, expertise, and time constraints. Decisions on service offerings are driven by need and considered for development with the help of an advisory committee. The GPCL are often the sole provider for procedures utilizing prohibitively expensive equipment that also may have a limited useful lifespan. In some cases, a technology becomes very commonly used and the most prudent course of action is to disseminate the process beyond a centralized core. For example, in the case of microarray technologies, the initial commercial technologies were extremely expensive and unproven. Custom array technologies were favored and purchased and used with great success by early standards. Within a short time, the price of Affymetrix systems dropped significantly, and their use became a more sensitive, validated and cost effective approach. An initial Affymetrix system purchase was supported by the Senior Vice Chancellor for the Health Sciences, as was an upgrade to the system. By making this available in a centralized Core, early duplicative services were avoided. As usage grew and diversified, and cost became less of a concern, newer systems were purchased by other campus entities. As another example, after Real Time PCR was available in the Genomics core, the cost of instrumentation decreased and the demand skyrocketed. Eventually, some investigators purchased instrumentation for their own laboratories, in consultation with, and training by, GPCL technical staff. Other investigators still use the Core services.

The Genomics and Proteomics Core Laboratories are active partners with both investigators and facilities across campus. Most notably, they has strong ties with two facilities at the University of Pittsburgh Cancer Institute. The Genomics Core works with the UPCI Clinical Genomics Facility to help transition basic research technologies into translational, cancer-focused research. Similarly, the Proteomics Core works with the UPCI Clinical Proteomics Facility; in particular, all requests to the GPCL for proteomic analysis of serum samples are forwarded to the Clinical Proteomics Facility. In 2004, the U.S. Department of Defense initiated funding for collaboration between the Proteomics Core Laboratory, the University of Pittsburgh Cancer Institute, and the Windber Research Institute. The Windber Research Institute has a comprehensive program focused on "high throughput 'parallel' characterization of gene and protein expression changes associated with cancer, genetic disorders and metabolic diseases."<sup>1</sup> Spanning basic to translational to clinical research, this collaboration leverages the basic proteomics research conducted in the Core with the clinical data obtained at UPCI and Windber to advance the analytical methods that can be used in clinical diagnostics.

The GPCL are funded through a combination of hard money support from the Senior Vice Chancellor for the Health Sciences, fee-for-service income, and targeted support for services from grants. The cornerstone of the fee-for-service is a rigorously-analyzed, fully-burdened, cost measure fiscal analysis. The University of Pittsburgh has prioritized this critical success factor by charging the Planning and Analysis team of the Department of Finance to work directly with researchers to assure the validity and reliability of the cost measures. Each analytical capability of the GPCL is taken individually and analyzed in the context of overall laboratory operations to determine actual costs. Each process is broken down into cost segments based on personnel time, equipment usage, supplies, administrative costs, and indirect costs. Each cost is analyzed considering material and time sharing, billable hours and overhead. Final costs reflect true operational costs. The following diagram summarizes the revenues that have supported the GPCL over the past eight years. Funds to purchase capital equipment have been provided by the Senior Vice Chancellor for the Health Sciences, as have been additional hard money funds to support salaries and other infrastructure costs. As is evident from the diagram, the percentage of the total budget that derives from fee-for-service charges has grown dramatically, indeed, the salaries of the majority of the technical personnel are now supported through this funding mechanism. The grant revenue is applied to the costs of services needed by investigators whose research is supported by the respective grant. While the funding for the GPCL from resources other than those provided by the Senior Vice Chancellor for the Health Sciences continue to grow, these data also clearly indicate the explicit commitment that the Senior Vice Chancellor has made to the viability of this critical core facility.

The Director of the GPCL is Paul Wood, M.S., who has been with the facility since its inception as the Center for Genomic Sciences. Fourteen full time technical staff perform the bench work within the GPCL, including a quality control manager, a Genomics Laboratory Supervisor, and a Proteomics Laboratory Supervisor. The GPCL also employ an administrator, a secretary, and two systems analysts. The GPCL act under the guidance of scientific directors for both the Genomics and Proteomics Laboratories; these faculty members, each expert in the relevant fields, provide both general scientific advice and input into project and technology development. In addition to his overall administrative responsibilities for the GPCL, Mr. Wood is the liaison between the Laboratories and investigators who are preparing grant applications that propose the utilization of the core

facility; he is the liaison with the manufacturers of Genomics and Proteomics equipment, and he works with the managers, directors, administrator, and senior administration in the Office of the Senior Vice Chancellor of the Health Sciences to enhance overall efficiency, including the procurement of equipment that allows the facility to remain at a state-of-the-art level. In addition to their technical or administrative responsibilities, the staff members of the GPCL also are involved in educational activities. Primary contacts have been named for each experimental process; thus, prospective users of the GPCL know with whom to meet in order to be educated as to services available and as to the investigators' responsibilities in sample preparation and data analysis. These primary contacts are responsible for including any other appropriate staff member in these early discussions so as to ensure that the best possible information is provided to an investigator and to ensure that all staff are informed about any project on which they will be working. They also provide the technical input for the GPCL website, including the development of standard operating procedures that need to be followed by investigators during sample preparation.

Since 2001, the GPCL has sponsored 21 technical seminars given by representatives of a wide range of Genomics companies, with an average attendance of 28 scientists; nine technical seminars focused on Proteomics technologies have had an average attendance of 15 scientists. In addition, two GPCL-wide open houses have been sponsored at which seminars were presented by GPCL technical staff members, investigators from the University of Pittsburgh Academic Health Center, and representatives from Genomics and Proteomics companies. The 2003 Open House was attended by 300 scientists, and the 2005 Open House was attended by 450 scientists. The GPCL have also organized and hosted a two-day, hands-on training exercise for students in the Molecular Biophysics III course (School of Medicine doctoral program), and they have hosted an overview presentation for residents and fellows during a summer research course.

#### Other cores at the University of Pittsburgh Academic Health Center

As discussed briefly above, there are many cores at the University of Pittsburgh Academic Health Center that do not fit within the working definition of *core facility* but that are, nonetheless, valuable components of the academic research enterprise. From conversations with the investigators who head many of these cores, it is clear that their use could be broadened to a wider range of investigators than is currently the case. It is all clear that some of these cores are, at least in part, duplicative of each other. This results, at least in some cases, in inefficient utilization of resources and, potentially, unnecessary delays in research productivity during equipment failures and maintenance. A major challenge for the Translational Technologies and Resources Core will be to create a framework that minimizes redundancy of efforts across the institution while maintaining individual, center, department, or school autonomy, as appropriate. This challenge is addressed by Specific Aims (2) and (3) of the TTCR.

## **CORE DESIGN and METHODS**

### Proposal to Achieve Specific Aim (1)

With the rapid pace of scientific discovery, fueled by the revolutionary changes in information technology, computer science, nanotechnology and miniaturization, robotics, laser technology, coupled with theoretical developments in areas ranging from quantum physics to systems biology, there is a corresponding acceleration in the pace at which new tools for biomedical research are developed. One of the primary challenges that academic research institutions face is determining when, how, and with what resources such new research tools should be provided to its investigators. Common questions that confront the institution and its investigators when considering research resources or new technologies with the potential to be broadly applied include:

- What new technologies (and/or) expertise are under the greatest demand and worthwhile to provide as core services?
- Are those technologies at a sufficient stage of development that they can be provided on a service basis?
- What capacity should the institution establish at any given time for a given technology?
- What additional institutional resources are required to support that technology (including consultation, education, regulatory, and informatics support)?
- How does one foster the appropriate use of the technology throughout the research community?
- When should the institution allow a technology to migrate out of a core facility and become a distributed, independent resource?

The Translational and Technologies Resources Core will support the development of new core facilities that are broadly needed by CTSI investigators, that are at sufficient stages of development to be offered as core services, and that will have the significant impact on the research progress of the CTSI community as a whole.

In the past, the core facilities that have been supported by the Senior Vice Chancellor for the Health Sciences were developed because a broad spectrum of investigators from across the health sciences expressed their desires and needs to have the relevant services available on campus. When ideas for such cores are first broached, it has been the responsibility of Michelle S. Broido, MD, the Director of the Office of Research, Health Sciences and the Associate Vice Chancellor for Basic Biomedical Research, to determine how extensive the interest is in such resources. If it has been determined that the need is broad, Dr. Broido has worked with representatives from the interested community to develop a proposed model for the operation and funding of the facility. The resulting model has then been discussed with the Senior Vice Chancellor for the Health Sciences and the Associate Senior Vice Chancellor for Administration, Health Sciences, and, with iteration, a business plan for establishing and running the facility has been developed and approved.

**The CTSI will provide funds for the development of new translational core facilities.** Proposals for these facilities may originate from any of a number of sources within the CTSI and the health sciences community. Consistent with previous experience at the University of Pittsburgh Academic Health Center, concepts for new translational core facilities will likely arise from grassroots expressions of interest. A focused session at the CTSI “Synergies in Health Research Day” will provide a platform for discussion of these ideas and will likely initiate the development of new concepts. *It can also be anticipated that techniques/tools/methodologies developed under the Novel Clinical and Translational Methodologies Core may eventuate in proposals for core facilities.* In addition, members of the CTSI Steering Committee, the CTSI Executive Committee, and the Internal multidisciplinary Advisory Committee, because of their broad perspectives across the CTSI network, will likely have suggestions for core facilities that would support a large cadre of CTSI members. Further, the CTSI Translational Technologies and Resources core, working through the Office of Research, Health Sciences, will actively solicit brief concept proposals for new core facilities six months before funding might be available. Following the model that has worked in the past, the Office of Research, Health Sciences will explore the breadth of interest in the proposed cores, both through personal contacts and working through an online survey developed and managed by the Center for Clinical and Translational Informatics. Because participation in such a survey will have impact on the future allocation of CTSI resources, robust response to the survey may be anticipated. Those ideas for which there is wide support will be reviewed and prioritized by the CTSI Steering Committee, the CTSI Executive Committee, and the Internal Multidisciplinary Advisory Committee.

In each year, the funding available for the development of new core facilities under the TTRC will be \$. Depending on the specific equipment, personnel, and operating needs for the core and the amount of **subsidization to be provided by the Senior Vice Chancellor for the Health Sciences**, the TTRC will provide support for up to two years. Provision of such support will not be forthcoming unless a business plan that addresses both core facility startup and the transition of its support from hard money to income from fee-for-service and grant revenues is approved by the Senior Vice Chancellor for the Health Sciences and the Associate Senior Vice Chancellor for Administration, Health Sciences. Responsibility for the development of such a business plan will fall to the Assistant Vice Chancellor for Strategic Planning and the Associate Vice Chancellor for Basic Biomedical Research, who will serve as co-directors of the TTRC, in conjunction with representatives from the CTSI community. Responsibility for the evaluation of the business plan for purposes of determination of CTSI funding to be allocated will rest with the CTSI Steering Committee and the CTSI PI. Key criteria will be

- Breadth of need by CTSI investigators;
- Maturity of development of technologies sufficient to be offered as a core service;
- Impact of the technologies on the research progress of the CTSI community as a whole.

Currently, two concepts for new centralized core facilities are under evaluation at the University of Pittsburgh Academic Health Center. The ideas for each are still embryonic, and the breadth of interest has not yet been ascertained. Whether or not either would rise to the level of a CTSI core facility is undetermined. The two concepts are:

- **MicroRNA Core:** The study of MicroRNAs (miRNAs) has revolutionized the central dogma of biology and is beginning to open up a new world of molecular networks. miRNAs are small (~22 nucleotides) RNAs that

mediate post-transcriptional silencing of genes by base pairing with target messenger RNAs (mRNAs). miRNAs are present in organisms as diverse as viruses, flies, worms, plants, and humans, where they likely regulate thousands of genes. miRNAs have been shown to play a key role in many physiologic and pathologic conditions both in humans and other organisms<sup>2,3</sup>. The lack of miRNA-related resources and expertise in this new field of biology has prevented investigators at the University of Pittsburgh Academic Health Center from incorporating miRNA studies into their research. University investigators are currently engaged in discussions with the Senior Vice Chancellor for the Health Sciences, the Associate Vice Chancellor for Basic Biomedical Research, and the Director of the Genomics and Proteomics Core Laboratories about a potential core facility for miRNA studies. The Senior Vice Chancellor has agreed to support preliminary explorations of feasibility, but there has not yet been a commitment to develop a core facility. It may eventuate that the miRNA “core” will be imbedded in the Genomics and Proteomics Core Laboratories, it may be a collaboration between the GPCL and the Clinical Genomics Facility at the UPCI, or it may be an independent facility. Further study is needed to determine the most appropriate organizational structure for providing miRNA capabilities to University investigators.

- **Human Gene Therapy Applications Laboratory:** The Human Gene Therapy Applications Laboratory (HGTAL) at the University of Pittsburgh was established in 1992 by the Senior Vice Chancellor for the Health Sciences and financed through the School of Medicine to produce clinical grade vectors for human gene therapy applications. Recently, the laboratory was renovated using School of Medicine resources to expand its capabilities including the manufacture of additional vector systems that include herpes simplex virus (HSV) for treatment of cancer and chronic pain. This new direction has led to reorganization of the facility with new leadership. New standard operating procedures to support the HSV vector manufacturing have been put into place and additional processes and audits have been set into motion to ensure compliance with Current Good Manufacturing Practices (cGMP) since such academic facilities are now subject to this level of regulatory compliance. The Laboratory also has a pre-clinical vector manufacture capability and has stock piled hundreds of vectors for use in pre-clinical studies throughout the United States. The expanded activities of the HGTAL and its need to maintain staff and day to day operations is quite expensive and funding levels are currently inadequate to provide the requested level of service by University of Pittsburgh investigators. Note, for example, many gene vectors require special design and construction, and production for use in the laboratory requires the expertise resident at the manufacturing facility. It has yet to be determined if the demand from University investigators for HGTAL services is sufficient to warrant an investment from the CTSI to develop the HGTAL as a CTSI core facility.

Any CTSI Translational Resource core that is developed will be expected to evolve in a manner similar to the evolution of the Genomics and Proteomics Core Laboratories (*vide infra*). Existing methodologies will expand or contract and new capabilities added as the needs of the CTSI community change and as the relevant technology develops. This expectation applies to the two possible future cores described in the examples, above.

#### Proposal to Achieve Specific Aims (2) and (3)

Achieving Specific Aim (2), the coordination of local cores with overlapping function, will first require a focused effort to gather information about the existence of such cores. While much of this information has already been gathered through a collaborative effort between the Assistant Vice Chancellor for Strategic Planning and staff in the Office of Research, Health Sciences, the data gathered provide a “snap shot” in time. Thus, achieving Specific Aim (2) requires both that baseline, “time zero” data be acquired and that a process for maintaining up-to-date data be developed and implemented. Baseline data will need to be gathered through systematic, but personal, contact. This can best be achieved by staff within the Office of Research, Health Sciences, as that office has access to the comprehensive research funding data for faculty within the schools of the health sciences, it has good working relationships with the research administrators in the individual departments and schools, and it, in itself, is viewed as a resource for providing information about available infrastructure by investigators across campus. The information to be gathered will include, but not be restricted to:

- capabilities
- usage history
- local quality control and standardization efforts
- level of adherence to national and international standards for quality control and standardization
- requirements for domain-specific expertise

- supplies needed and reliability of suppliers
- publication and funding records

This information will be made available to CTSI members on request through the Online Research Community (ORC) portal that is part of the CTSI Center for Clinical and Translational Informatics. (The Online Research Community [ORC] is an electronic infrastructure that will transform communication, information sharing and access to education for our research community, through directories of research-related entities, intelligent information routing, and training resources; see the CCTI section for details.) This information will also be selectively “pushed” to targeted CTSI members. Once the baseline data are available, updates will be requested from each core at 12 month intervals. Access to CTSI funds for possible enhancements of these cores will be regulated in correlation with the promptness in which the updated information is provided. This effort will serve CTSI members in several ways. Before CTSI members develop new local cores, they will have a mechanism by which they can determine whether a relevant or duplicative resource is already available. This will allow better informed judgments as to whether to outsource to another core, establish a new core, or form a research partnership (for example, by providing funding for a domain expert from another core).

The second step in achieving Specific Aim (2) is also manpower intensive, and it must be achieved by someone with scientific and research experience who can communicate effectively with the scientists and administrators who run these cores, understanding their goals and needs, and serving as a diplomatic “matchmaker,” when appropriate, for local cores that have overlapping purposes. Initially, the leadership of each core identified in the baseline set of data will have to be contacted, and it will be crucial that any proposed consolidation of effort not compromise the net scientific capabilities available to investigators. Similarly, new cores will need to be incorporated into the process. Teresa Brosenitsch, PhD, a scientific staff member within the Office of Research, Health Sciences, has the knowledge and demonstrated tact and diplomacy to take the lead responsibility for the activities necessary to achieve appropriate integration of the local research cores.

Specific Aim (3) is focused on the need to educate the CTSI research facilitators and, by extension, CTSI investigators, about the core facilities and local cores that are available. Coordinated educational programs will inform students, staff, postdoctoral fellows, junior faculty, established investigators, the research facilitators, and members of CTSI leadership committees about the existence and capabilities of the research cores. These programs will have multiple benefits, including direct impact on achieving Specific Aims (1) and (2).

Educational efforts will include electronic and instructor-based modalities. Web development support for online tutoring and training will be developed in close coordination with the CTSI Research Education, Training and Career Development program, utilizing the resources of the ORC portal mentioned above. These online educational resources will be available through the ORC in a searchable fashion and in a way that links each one bidirectionally to the relevant core(s) or core facility(ies).

As described in the CTSI Pilot and Translational Studies Core section of this application and in the description of the GPCL, above, educational programs based on lecture and workshop modalities are already incorporated into some of the activities on campus that support translational research. A regular program of seminars and workshops will be conducted by subgroups of cores or by industrial representatives who sponsor technologies that are available in the cores. Invited speakers will include faculty with strong domain expertise who are willing to provide consultation in their domain areas.

### **Evaluation Plan.**

The expected outcome from Specific Aim (1) of the Translational Technologies and Resources core will be the establishment of core facilities that bring new and powerful laboratory-based technologies to a broad spectrum of CTSI investigators who might otherwise not have access to such technologies. The expected outcome from Specific Aims (2) and (3) is a more efficient use of research resources than is currently the case. The evaluation of progress with regard to Specific Aim (1) will be an assessment of the adherence to the business plan development for any new core facility and, once such a core is operating, evaluation of the number of investigators who use such a core and the breadth of disciplines which are represented by the users, as well as analysis of user satisfaction surveys. Evaluation of Specific Aims (2) and (3) will include a determination of the extent of appropriate consolidation of cores, traffic on the web-based communication tools, participation in the education programs, and the ability of the research facilitators to refer CTSI members to the appropriate cores. For details of the evaluation process please see the CTSI Evaluation section of the application.

### **Proposed Timeline for Implementation.**

Year 1		Year 2	Year 3	Year 4	Year 5
Baseline data on all existing translational cores will be acquired		Existing and new cores will be surveyed annually to assess core capabilities, usage, and productivity			
Concept proposals solicited and reviewed	1st new core facility initiated	New core facility will be funded as it prepares to transition to a non-CTSI funding mechanism	New CTSI core facility will no longer depend on CTSI-funding		
		Concept proposals solicited and reviewed	2nd new core facility initiated	2nd new core facility will be funded as it prepares to transition to a non-CTSI funding mechanism	New CTSI core facility will no longer depend on CTSI-funding
					Concept proposals solicited and reviewed
					3rd new core facility initiated

**Summary: Transforming the Translational and Clinical Research Enterprises.**

The portfolio of core facilities already in existence at the University of Pittsburgh provides a solid foundation on which to model the development of new core facilities. New CTSI core facilities will only be developed if they are responsive to a need articulated by a breadth of CTSI members, and they will be focused on technologies that are at the forefront of new research tools. Consolidation of the smaller cores that support local research activities will minimize the unnecessary duplication of scarce resources and will allow for expansion of capability. The educational programs will raise awareness of useful research methodologies among CTSI investigators.

**Literature Cited:**

1. The Windber Research Institute. Genomics and Proteomics Program page. Available at: [http://wriwindber.org/services\\_expression.html](http://wriwindber.org/services_expression.html). Accessed March 20, 2006.
2. Ambion, Inc. Web Resource Pages: miRNAs: Definition & Overview, Available at: [http://www.ambion.com/techlib/resources/miRNA/mirna\\_intro.html](http://www.ambion.com/techlib/resources/miRNA/mirna_intro.html). Accessed February 6, 2006.
3. Alvarez-Garcia, Ines and Miska, Eric A. (2005) MicroRNA functions in animal development and human disease. *Development* 132, 4653-4662.



***Transforming Health Practice:***  
**CTSI Community PARTners (Partnering to Assist Research and Translation) Program**

The absence of functional collaboration among the research, practitioner, and lay communities contributes to the inefficiency of the research enterprise with respect to enhancing the health of the population. Failure to proactively enlist community involvement in clinical research agendas results in difficulty meeting recruitment goals, which, in turn, delays timely completion of clinical trials. In addition, there is ample evidence that new research findings are slow to enter the practice environment. Multiple reasons have been postulated, and they tend to center upon the limited and isolated relationships between the communities of interest and the academic research enterprise. This absence of ongoing meaningful relationships contributes to a lack of trust and confidence between the community and researchers, independent of the pursuit of the goal of enhancing the health of the population, and incomplete communication, if not miscommunication, about research and research findings.

The University of Pittsburgh Clinical and Translational Sciences Institute (CTSI) has as one of its primary functions the development of a sustainable institutional program to engage the community in clinical and translational research. The CTSI broadly defines the community as comprising the 1) lay community, 2) health provider community, and 3) community of research investigators. To that end, the Community PARTners (Partnering to Assist Research and Translation) Program will be established to support the engagement of these communities in collaborative relationships that will facilitate trust and ongoing communication. The broad objective of this program is to foster ongoing communication and build informed communities that collaborate in the generation of research hypotheses, conduct of research studies, and translation of research findings into practice.

The **specific aims** of the Community PARTners Program are to:

- 1. Develop a “research informed lay community” that actively participates in (a) clinical research studies, (b) translation of research discoveries to individuals and populations, and (c) the development of clinical and translational research agendas;**
- 2. Develop a “research informed multidisciplinary health professional community” that actively participates in (a) evidence-based practice that fosters the translation of research findings, (b) study participant recruitment and (c) conduct of clinical research as well as the development of clinical and translational research agendas; and**
- 3. Develop “community-informed researchers” who foster the performance of clinical and translational research by (a) educating, (b) communicating with, and (c) partnering with lay and multidisciplinary health professional communities.**

The CTSI postulates that the development of research-informed lay and health provider communities and community informed research investigators will facilitate: 1) the recruitment of subjects into clinical research studies; 2) the translation of research discoveries to individuals, communities and populations; and 3) the development of research agendas that are relevant to residents of western Pennsylvania. Furthermore, the CTSI hypothesizes that this fundamental principle of community engagement will increase the standard of health care and promote translation of research discoveries in the region by promoting the practice of evidence-based health care in the community.

## **BACKGROUND**

The “golden years” of clinical research that occurred between the end of World War II and the early 1960s focused on patient-oriented clinical research.<sup>1</sup> The interrelationship between clinical care and research during these years resulted from continuous interactions among physicians, scientists, and patient-subjects and a two-way movement between the clinical and laboratory settings.<sup>1</sup> This stemmed from the close proximity of basic science laboratories, clinical wards, and physiologically based research units, which, in turn, led to a social organization of and an academic home for clinical research.

During the last three decades, the focus of clinical research has transformed from the study of the sick<sup>1</sup> to more comprehensive studies and trials in human subjects.<sup>2</sup> Clinical research has also become an integral component of the broader applied discipline of translational science. Translational science includes two segments: 1) application of discoveries generated during research in the laboratory and in preclinical studies to the

development of trials and studies in humans and 2) enhancing the adoption of best practices that are identified by clinical research in the community.<sup>3</sup> Therefore, the ultimate goal of clinical research and translational science is to improve health as well as prevent and treat disease among individuals, communities, and populations. Thus, recruitment of subjects takes place among inpatients, outpatients, healthy and at risk populations as well as disease-affected individuals. Broadening of the definition of clinical research has been associated with the rapid expansion of the research enterprise and a demolition of the historical academic home for clinical research.

Yet barriers exist for both the conduct of clinical research and its translation into practice. Investigations of barriers to clinical research indicate that patients are hesitant to participate in research studies due to study demands (e.g., appointments, procedures), travel, costs, preconceived preferences for a particular treatment, concerns about the uncertainty of treatments, and concerns related to the consent and regulatory processes.<sup>4</sup> Community barriers include skepticism about equality in partnerships, historical inequality in access to resources, competing demands on time and resources, and knowledge and skills in the research process among community members.<sup>5</sup> These barriers are particularly relevant to minority, underserved, uninsured, poor, and rural communities, all of which have lower participation rates in clinical research.<sup>6</sup> Additional barriers include ineffective communication between patient and provider, community infrastructure, lack of outreach, and the lack of understanding about the value of research in improving health.<sup>6</sup> Additionally, these populations are more inclined to distrust academic medical centers as a result of historical and existing inequities in healthcare, health disparities, under representation of minorities in health professions, and history of mistreatment in clinical research studies (e.g., Tuskegee experiment). In general, trust in the health care system is low at this point in time, and the public does not distinguish between clinical research and the health care system.<sup>7</sup>

The delay or avoidance of adoption of research findings in practice also constitutes a significant problem. It is estimated that there is a 10-20 year lag in incorporating research findings into routine clinical practice.<sup>8</sup> Moreover, it has been reported that only about 60% of patients receive recommended care for chronic conditions.<sup>9</sup> Multiple factors influence the slow pace of adoption of research findings.<sup>10</sup> These include the perceived benefit of the findings, how well they fit with current needs and practices, the level of complexity, whether the findings can be tried/tested with a small sample of patients, and whether the implementation can be observed.<sup>3</sup> Others include concern about the adequacy of resources, the similarity or difference in the situation of practice, and the necessity to strive for those goals (e.g., accessibility, credibility and expectations).<sup>11</sup>

Development of relevant partnerships is fundamental to addressing these barriers. Engagement of the lay community can help to dispel the problems with trust, access, and knowledge and will allow investigators to address community concerns regarding resources, time, and priorities. A complementary approach to recruitment of subjects from the community employs the development of partnerships between academic health centers and community-based professionals.<sup>12</sup> This entails not only informal partnerships but education of the practitioners about research design and the value of research.<sup>13</sup> The development of both community and health professional networks to promote clinical research and its translation have common fundamental elements.<sup>5</sup> Academic health centers must provide the community (lay and health provider) with a/an: 1) trusting bi-directional relationship; 2) education as to the benefits and risks of research studies; 3) sustainable benefits (e.g., services, resources, access to state-of-the-art health care); 4) knowledge about research ethics and protection of human subjects; 5) education about the value and benefits of research and its findings; and 6) infrastructure to support the performance of research in community settings. It must also provide investigators with the skills and knowledge to communicate with diverse communities. Each of these elements requires long-term university educational, financial, and logistical (e.g., information technology) commitments to the lay and health provider communities.

### **Current State**

The University of Pittsburgh is fortunate to be home to many novel and successful community engagement initiatives and resources. The intent of the CTSI is not to eliminate or replace them, but to leverage their strengths in the establishment of a centralized, coordinated engagement program that will eliminate barriers between schools, disciplines, institutions, and communities. This section describes the following: 1) the community surrounding the University of Pittsburgh; 2) selected research centers and existing programs at the University of Pittsburgh and the UPMC that serve as examples of best practices in community engagement; and 3) limitations of the current state that impede community involvement in clinical and translational research.

The Design and Methods section describes how these resources will be transformed into a program that will expand the capacity of the CTSI to engage the lay, health professional, and research communities in collaborative partnerships that will advance the discipline of clinical and translational research.

### **The Surrounding Community**

The University of Pittsburgh is centrally located in Pittsburgh, a neighborhood-centric urban community. The community of interest encompasses a diverse array of persons and organizations. County statistics reveal that Pittsburgh contains a well-educated, aging population residing in small households. Disability rates (14%) are higher than average.<sup>14</sup> The population of approximately 1,209,484 (county), is 52% female and 17.3% over 65 years of age, compared with a national average of 12%.<sup>15</sup> Over 17% are persons of color, with nearly 1/3 of the city itself. The community is well educated, with 90% having a high school degree and 31% having a college degree or greater. Approximately 11% of the population is below the poverty level. Nearby, and within the healthcare catchment area are several small rural counties where the proportion of elderly is higher, as is the proportion who are disabled, and education levels are lower.

### **Selected Research Centers and Existing Programs**

**Graduate School of Public Health (GSPH)** Among the community engagement programs housed in the GSPH, is the Center for Minority Health (CMH), a lead entity within the schools of the health sciences to coordinate the academic, research, and service activities of faculty and students who deal with issues relevant to minority health and health disparities. In this capacity, the center's evidence-based interventions are closely tied to the National Initiative to Eliminate Racial and Ethnic Disparities in Health and the nation's health promotion and disease prevention agenda established in *Healthy People 2010*.<sup>16</sup> The center's community health promotion and prevention work is channeled through the EXPORT Health Community Outreach and Information Dissemination Core. The CMH also works closely with research investigators to help build their capacity to increase the participation of underrepresented populations in research. The CMH will continue to be a resource to the research community and will be called upon to offer consultation on reaching the minority populations in the area.

**School of Dental Medicine (SODM)** The Center for Oral Health Research in Appalachia (COHRA) is a collaborative effort between the University of Pittsburgh's Center for Rural Health Practice and the SODM. Viewed from an ethnography perspective, Appalachia constitutes a unique American culture, often referred to as the "forgotten minority." It has been long recognized that children and adults in Appalachia, have significant oral health disparities compared with the general U.S. population. Oral health problems develop early in life among Appalachians, resulting in a trajectory of poor oral health over the life course. The overarching mission of COHRA is, through enhanced understanding of the nature of the person-environment interaction, to inform and implement effective community-based prevention programs aimed at the reduction of oral health disparities. To accomplish this mission, COHRA has been organized around a unifying theme that can be summarized as a multifactorial, developmental characterization of person-environment interactions in children that result, over their life course, to the development of oral disease liability. Mindful of the need for culturally appropriate and targeted intervention at the community level, COHRA is strongly linked to the Appalachian community through organizations such as the University of Pittsburgh's Center for Rural Health Practice and the West Virginia Rural Health Education Partnership. COHRA will serve as a template for the engagement of rural communities in CTSI activities.

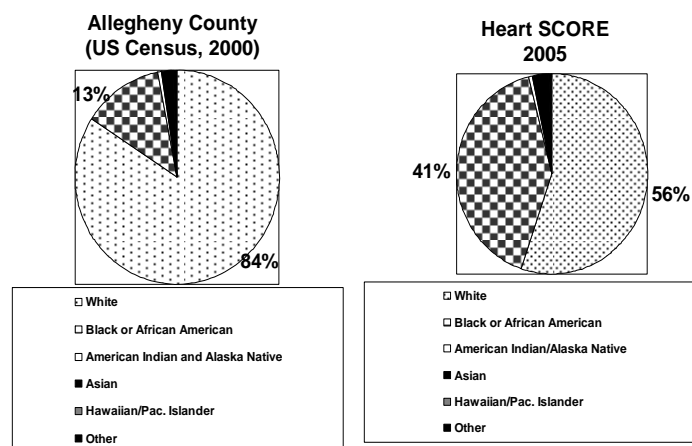
**School of Health and Rehabilitation Sciences (SHRS)** Operated under the auspices of the SHRS, the University of Pittsburgh Rehabilitation Engineering Research Center (RERC) on Telerehabilitation serves people with disabilities by researching and developing methods, systems, and technology that support remote delivery of rehabilitation and home health services for people who have limited local access to comprehensive medical rehabilitation in outpatient or community-based services. Research and development activities are in the areas of telerehabilitation infrastructure and architecture; telerehabilitation clinical assessment modeling; teleassessment for the promotion of communication function in children with disabilities; remote wheeled mobility assessment; behavioral monitoring and job coaching in vocational rehabilitation; and remote accessibility assessment of the built environment. Education and training initiatives are integrated into the research and development processes in order to develop expertise among consumers and providers. The RERC will serve as a consulting resource for investigations that utilize telehealth technologies in the collection of data or delivery on interventions with distant or isolated populations.

**School of Medicine (SOM)** Heart Strategies Concentrating On Risk Evaluation (Heart SCORE) is a large scale community based participatory research program that was developed by Steven Reis, MD (CTSI Principal

Investigator) to address Healthy People 2010's Goal of Eliminating Health Disparities.<sup>16</sup> The objectives of this Commonwealth of Pennsylvania funded study are to: 1) improve CVD risk stratification among African Americans in western Pennsylvania; 2) identify CVD disparities based on race and socioeconomic status; 3) evaluate biological mechanisms for population differences in cardiovascular risk; and 4) implement and evaluate a multidisciplinary community-based intervention program to decrease CVD risk in high-risk populations. Heart SCORE was designed as a prospective cohort study seeking to enroll 2,000 residents of western Pennsylvania with equal representation of Caucasian and African American subjects. Nested within this cohort study is an intervention study that evaluates a multidisciplinary culturally sensitive community-based behavioral modification intervention to reduce CVD risk. Ongoing recruitment is occurring in partnership with several community partners including the Urban League of Pittsburgh, Metro-Urban Institute Office of Applied Religion (MUI-OAR) of the Pittsburgh Theological Seminary, Center for Healthy Hearts and Souls, the Jewish Health Care Foundation, a network of more than 30 local churches and community organizations, and community-based physicians and health professionals.

As a result of the trust that has been established within this investigator-initiated university-community partnership, Heart SCORE has recruited a cohort of nearly 1900 study participants with a distribution of minority participants that is more than threefold that of Allegheny County (see Figure 1). This study has not only demonstrated the success of a community-based participatory research program in Pittsburgh led by the CTSI principal investigator, but has also provided data that will reduce race-related disparities in CVD (manuscripts in preparation and submitted). From a service perspective, Heart SCORE's recruitment program has provided educational and health screening benefits to more than 2000 individuals who live in underserved communities surrounding the University of Pittsburgh. Heart SCORE will serve as a model of community participatory research in establishing community-research partnerships.

**Figure 1.** Heart SCORE Recruitment Data (n=1881).



**School of Nursing (SON)** The SON initiated an extensive program in evidence based practice (EBP), which provides the foundation for the education of nurses at a variety of levels (BS, MS, PhD). Three levels of education are included. First is the foundational education in EBP, which includes basic statistical skills, critical evaluation of the research literature, strategies for accessing the literature, and identifying and using patient preferences and values in designing care. The second level focuses on the development of expertise in EBP and redesigning practice. This includes more advanced skills in interpretation of statistical analysis, evaluating and comparing bodies of evidence for utility in practice, and designing and evaluating evidence-based protocols within the practice setting. The third level prepares the student for contributing to the science underlying practice. In addition to developing a greater understanding of design and analysis methods, this enhances skills in activities such as performing meta-analyses, evaluating evidence and practice to determine the next important questions, and conducting research. To support this initiative, faculty within the SON have developed a number of "tool kits." Criteria and guided forms have been developed to review literature from various design perspectives, such as randomized clinical trials, observational studies, and qualitative studies. Identification of sources of information about more common cultural, ethnic, religious, and other personal characteristics have been identified to support learning about the value and preference issues that need to be considered in planning care. A third tool kit includes information on conducting literature searches, with case study examples that incorporate patient characteristics (e.g., cultural and religious practices) and clinical findings (e.g., co-morbid conditions).

The ability to educate students is important for the future of health care and for clinical research and translation. However, it is also important to promote the use of research findings among current practitioners.

Given the long delay in adoption of research findings in practice, 10 to 20 years in health care,<sup>9</sup> passive approaches are likely to be unsuccessful. Therefore, another element of this initiative is to examine the barriers to adoption of EBP principles in current clinical practice and to determine models of successful adoption. Therefore, several activities are underway. A survey to examine institutional and individual readiness for EBP supported care management is being undertaken in five rural hospitals. Preliminary data suggest that the education of the nurses in practice did not include research principals in many cases and that the perception was that the use of research did not apply outside of academic health centers. Following a more inductive approach to foster adoption of EBP principles in practice, nurses from one hospital have begun the process of interviewing patients post-discharge to determine the level of understanding and adherence to discharge instructions. At the time of this writing 92 patients have been interviewed. A facilitated review of the data collected will discover problems with post-discharge adherence (estimated to be about 50% based upon the current literature on adherence). A facilitated examination of a review paper on adherence interventions will identify improvements that can be made in discharge instruction, followed by a second post-discharge assessment of patients. If this strategy is successful, the process will be disseminated to other settings. If not, alternative strategies will be evaluated. Within the academic health center, faculty from the SON sit on a committee to develop evidence based protocols for care delivery. Concurrent with this initiative is the development and conduct of a continuing education series for practicing nurses at various levels, including advanced practice nurses and nurse educators. The SON is experienced in distance education throughout Western Pennsylvania, and this educational technology will be utilized to enhance the EBP program and to reaching a broader audience. This initiative will serve as the paradigm for a CTSI-based initiative to educate and promote adoption of research (i.e., EBP) among practicing clinicians from multiple disciplines.

School of Pharmacy (SOP) The SOP and the Rite Aid Corporation have partnered to develop four centers of excellence for medication therapy management and advanced pharmacy practice in Rite Aid pharmacies in the Pittsburgh area. Each Rite Aid Center provides this service in support of four to eight additional stores bringing the total number of Rite Aid stores where patients are served to 28 stores in the Pittsburgh Area. The Rite Aid Centers of Excellence all employ software developed by the SOP to capture information about the patient and outcomes in addition to the information normally captured about medications dispensed. This network will be expanded to eight regions nationally from fall of 2006 to spring of 2007. The Rite Aid Centers of Excellence provide a unique method for enrolling community-dwelling patients into clinical studies or patient registries.

Non-Health Science Schools The Center for Rural Health Practice at the University of Pittsburgh Bradford regional campus provides clinical researchers with access to rural communities and health providers as well as identifies and articulates research health issues that are relevant to rural America. The center is located in northern Appalachia and serves a six-county region in northwestern Pennsylvania. Its service area is characterized by disparities in socioeconomic status, health status, and access to care. Within this region, the center has been instrumental in the development of a regional healthcare network, the *Kinzua Regional Health Alliance*. The *Alliance* is comprised of the five non-UPMC affiliated hospitals serving this region and additional health providers such as home health agencies, nursing care facilities, paramedics, dentists, and other health personnel. Using this network, the center has conducted studies addressing the financial vulnerability of rural home health agencies and built an integrated community health database for health planning purposes. Other efforts include a study of rural health workforce shortages, hosting a research study site for the University of Pittsburgh's School of Dental Medicine's NIH-funded Center for Oral Health Research in Appalachia, conducting an employer-based health promotion initiative, and the development of rural terrorism preparedness trainings and resources. This healthcare alliance will work synergistically with the CTSI to identify facilities and participants for clinical trials and develop research programs that identify and reduce rural health disparities. The center also has access to ITV facilities that can be used to provide targeted training and education to rural health providers and support telehealth biomedical applications such as those that are being initiated by the School of Health and Rehabilitation Sciences. The interactive nature also allows for feedback from rural providers that can aid in the development of clinical research that is relevant to the rural population.

Centers for Research The University of Pittsburgh is fortunate to have numerous NIH supported centers of excellence addressing a variety of research programs. These programs provide a consolidated source of interdisciplinary investigators who are addressing clinical problems of relevance in the community, and most have educational programs in place for junior investigators. Table B.1 of this proposal contains selected

examples of NIH supported centers that will provide dissemination sites for programs developed by the Community PARTners Program, such as cultural sensitivity training, community communication, and other initiatives. The PARTners Program will, in turn, serve as a resource for the dissemination of center activities within the research communities and health professions communities.

**UPMC** The UPMC is the dominant health system in western Pennsylvania, having 45% of the market Share in Allegheny Count and 25.3% of the market share in its 29 county service area. The UPMC consists of 19 hospitals and 350 outpatient offices and specialized outpatient sites. Its institutions account for 3 million outpatient visits, 150,000 inpatient admissions, 350,000 emergency room visits, and one million home health care visits each year. (Additional details on the UPMC are in the CTSI Overview section and Tables B.2 and B3 of this proposal.) The UPMC has targeted specific initiatives within their regional institutions. For example, the UPMC has designated Braddock Hospital as its flagship hospital for leadership in working to eliminate health disparities within the region. This hospital was chosen based on its tradition of service to low income, minority communities located within its service area. The St. Margaret's Hospital, a suburban general hospital, has been designated as a center for Information Technology. Horizon Hospital, a rural community hospital, is participating in the nursing evidence-based practice initiative. Other areas of emphasis, including community and industry initiatives, exist throughout the system.

### **Limitations of the Current State**

The research enterprise at the University of Pittsburgh has an extensive long-term track record of the performance of clinical and translational research in the community. For example, the successful development of the polio vaccine by Dr. Jonas Salk and colleagues at the University of Pittsburgh in 1955 required the translation of the Salk team's basic science discovery by the performance of clinical studies in communities surrounding the university. This program formed the foundation for translation of the development of a vaccine that eradicated polio to national and international community practice. Numerous other examples exist. For example, studies on cardiopulmonary resuscitation have led to guidelines for the management of cardiac arrest. The Graduate School of Public Health has contributed to numerous large-scale multicenter trials that have informed health policy (e.g., the MRFIT and WHI studies). The School of Nursing has carried out studies on patient adherence in research and practice that have also informed the research agenda. The Schools of Health and Rehabilitation Science have contributed a bioengineering and rehabilitation perspective to mobility enhancements for the disabled. Despite these and numerous other examples of successful translation of basic research to the communities in Pittsburgh, university investigators continue to encounter barriers to clinical and translational research that are similar to those that are faced by most urban academic researchers across the United States. The clinical and translational research effort is further hampered by lack of a coordinated effort to engage the community in research activities as each investigator typically addresses these barriers independently.

The culture and neighborhoods surrounding the university limit the exposure of investigators to adjacent communities. These communities have diverse populations who are primarily socio-economically disadvantaged. Over 200 years of history has bred a long-term sense of distrust. In the recent past, however, the university has developed aggressive outreach programs to improve its relationship with and solicit guidance from surrounding neighborhoods.

Numerous barriers have been identified by representatives of the community and by multidisciplinary health practitioners within the community. Practitioners have expressed concerns about the burden placed on an already busy staff and practitioners, both in terms of participation in research initiatives as well as in investment in adopting findings beyond those recommended in accepted guidelines. Value associated with specific initiatives is not always perceived. Often the findings of the research itself are seen as not applicable to the practice setting, often due to the complex clinical pictures that patients present while studies often address a single dimension without attention to other conditions that may be presented by the research subject. Concerns exist about the diversion of patient care from the practice center. In addition, the conduct and utilization of research historically has not been a strong component of practitioner education. "Research tracks" in educational programs across the health sciences have separated the typical practicing clinician from the basic or clinical investigator. At times when efforts are made to disseminate research findings to practice, a uni-directional, linear approach is taken, ignoring the experience, setting, and knowledge of the practitioner in adapting findings to the unique setting. Furthermore, although the patient's experience of health care is multidisciplinary, elicitation of participation and dissemination of research findings is often within disciplines.

The University of Pittsburgh and UPMC have developed model programs to address these barriers. While these programs have had substantial impact on individuals, their overall community impact have been limited as a result of narrow scope (e.g., focus on specific disease entities or disciplines) as well as limited and cyclical resources. The impact and sustainability of these programs can be optimized by organizing them in the CTSI academic home using a multidisciplinary collaborative approach that has been supported by institutional, foundation, and federal funds. Therefore, a major objective of the Community PARTners Program will be to address the barriers to efficient clinical and translational research as a coordinated, collaborative activity.

### CORE DESIGN and METHODS

The development of an institutional program of community engagement in the CTSI is critical to sustaining the clinical and translational research enterprise at the University of Pittsburgh. The CTSI will transform the practice of fragmented and decentralized community engagement at the University of Pittsburgh to a coordinated institutional approach. This will allow resources to be pooled, committed investigators to be formally trained in cultural sensitivity and appropriate approaches to community engagement, and the community to have a "point person" to contact in their development of health-related programs. Accordingly, the Community PARTners Program will: 1) develop an institutional framework that will result in an effective, sustainable community engagement program; 2) identify and centrally organize existing decentralized "best practices" community engagement resources at the University of Pittsburgh and UPMC; 3) integrate existing programs into the new CTSI Community PARTner Program; 3) organize existing and newly developed community, health provider, and research investigator networks; and 5) address barriers to effective community engagement as they arise. This section will describe the administrative and operational foundation of the PARTners Program and then address the proposed activities for the three target communities.

#### Administrative and Operational Foundation

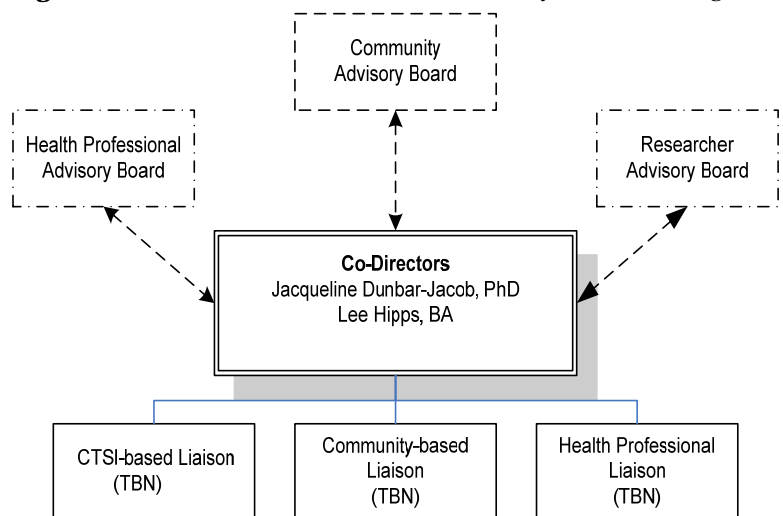
The Community PARTners Program will utilize an innovative administrative and operational foundation wherein there is representation from each of the communities of interest (Figure 2).

**Directors** The Community PARTners Program will be co-directed by a member of the CTSI (with experience as a health care provider and a researcher) and a member of the lay community. Shared leadership will foster a true sense of partnership and enhance the ability of the Community PARTners Program to meet its objectives.

#### **Jacqueline Dunbar-Jacob, PhD, RN, FAAN,**

has been involved in numerous community and clinical research activities. She is active within the community through participation in health improvement and workforce initiatives at local foundations as well as through workforce initiatives at the state level. She is currently a board member of three local organizations, including the UPMC Shadyside-Presbyterian Hospital, and is a participant in the UPMC vice-presidents for patient care services monthly meeting. She chairs the national advisory board of the Institute for Healthcare Communication, a national continuing education organization that delivers training in patient-provider communication. She is active in interdisciplinary professional organizations, including past-president of the Society of Behavioral Medicine and the Academy of Behavioral Medicine Research, which address the interplay of behavior and medical conditions, and past board member of the Society for Clinical Trials. She currently serves on two NIH advisory boards (DSMB of the Diabetes Prevention Trial, NIDDK) and chairs the Scientific Advisory Board of the roadmap measurement initiative, Patient Reported Outcomes Measurement System (PROMIS). She has served on three other NIH advisory boards: 1) the advisory board of the Hypertension Prevention Trial (NHLBI), 2) the DSMB of the Optic Neuritis Treatment Trial (NEI), and 3) the National Institute for Nursing Research advisory board as well as on numerous NIH working groups. She served as deputy director of the behavioral science group of the Lipid Research Clinical Program and

**Figure 2.** Administrative structure of Community PARTners Program.



behavioral science advisory during the design and feasibility phase of the Diabetes Control and Complications Trial. Her own research, which is clinical in nature and NIH funded, has actively engaged community practices in the recruitment of subjects for over 15 years. She is principal investigator for the NIH supported Center for Research in Chronic Disorders which focuses principally on adherence (patient, provider, investigator) and quality of life. She is currently project leader of the adherence and retention core of the Pepper Center. In addition, she leads the School of Nursing, including the EBP initiative, which was funded by the Robert Wood Johnson Foundation as an executive nurse fellow leadership project. She has secondary appointments in two of the health science schools.

**Lee Hipps, BA, Executive Vice President, Urban League of Pittsburgh** is a highly respected community leader with extensive experience in organizational management, strategic management, program development, and customer service. Mr. Hipps served as Director of Support Services for Magee-Womens Hospital, for nine years, during which time he gained expertise and skill in meeting the complex and often competing needs of health care institutions, health care providers, and community members. Mr. Hipps currently serves as the Executive Vice President and Chief Operating Officer of the Urban League of Pittsburgh, an organization that has played a central role as an advocate and direct service provider in basic human services in Pittsburgh since 1918. In addition to having an integral role in the logistical implementation of CTSI Community PARTner Programs, the Urban League will serve as a link between the CTSI and other community organizations. During his tenure at the Urban League, Mr. Hipps co-developed successful community-based participatory research programs with Dr. Reis, CTSI PI.

**Community PARTners Program Liaisons** Success of the PARTners Program relies heavily on the communication, interaction, and integration and use of resources across the three communities of interest. To that end, the Community PARTners Program will institute an operational foundation consisting of three types of liaisons, each with a focus on a specific community of interest: the **CTSI-based Community Liaison**, the **CTSI-based Health Professional Liaison**, and the **Community-based Liaison**. Each liaison will be responsible for interacting with his/her counterparts, the program co-directors, and the advisory boards to ensure the needs of their constituencies are addressed.

The **CTSI-based Community Liaison** will be an integral part of the CTSI-based Research Facilitator program (see the CTSI Overview section of this proposal) and will interact directly with researchers, university schools and departments, and UPMC to identify investigator needs that are relevant to promote community-based participatory research, clinical research in the community, and the translation of research to practice. A major role of the CTSI-based Community Liaison will be to establish and maintain a centralized repository of resources related to community engagement. This will be done by identifying existing community engagement programs as well as formal and continuing education courses related to community engagement, and evaluating their applicability for inclusion in the program repository. This liaison will also meet individually with investigators who are referred to them via the CTSI Research Facilitators to assess the investigators' needs and connect them with relevant resources. The CTSI-based liaison will be expected to work closely with the Health Professional and Community-based counterparts to facilitate requests brought forth by these liaisons by identifying and mobilizing resources within the university and UPMC environments. The CTSI-based Liaison will be responsible for identifying gaps in education, services, and resources and collaborating with the program directors and other CTSI cores in the development of methods to bridge those gaps.

The **Health Professional Liaison** will be a registered nurse with clinical research and education experience who will serve as an advocate for members of the multidisciplinary health professional community. This individual will be responsible for cultivating relationships with community-based health professionals and identifying and addressing their needs for educational programs related evidence-based practice and clinical research. A major responsibility of this liaison will be to coordinate the pilot Evidence-Based Practice (EBP) initiative that is outlined later in this section.

The **Community-based Liaison** will serve as an advocate for the lay community. This liaison will be a registered nurse who operates from the PARTners Continuity Clinic that is described later in this section. This individual will be responsible for performing selected health screenings and making referrals as well as



identifying needs and requests for education, services, or resources brought forth by the lay community. This liaison will work with other CTSI-based liaison counterparts to identify resources and orchestrate these programs.

**Advisory Boards** To ensure that the Community PARTners Program addresses issues of relevance to the target communities, three advisory boards will be formed to provide guidance on program activities.

The **Community Advisory Board (CAB)** will be established during year one. Members will be well-respected individuals from the community, and efforts will be made to ensure representation reflective of the demographics of the surrounding community. During the first six months, the CAB will meet monthly to develop a mission statement, establish goals, define roles and responsibilities of members, and establish mechanisms to evaluate and prioritize needs and requests related to the lay community. Subsequently, the CAB will meet semiannually to provide guidance with respect to the program activities and services that target the lay community. It will be responsible for programmatic direction, the development of programs, and interpretation, and response to program evaluations. The CAB will also provide advice about interactions with community-based organizations and foundations, and public programs that should be cultivated as program partners. It will be responsible for advising the PARTners Program as to specific operational issues relevant to the lay community. These issues include, but are not limited to, those related to seeking and responding to input from the community, the development of appropriate community-based programs (e.g., educational, services, research), funding priorities for community-based participatory research, and initiating and sustaining relationships between the CTSI and local community, foundation, organization, and governmental groups. In addition, the CAB will provide an annual evaluation of the activities of the Community PARTners Program.

*A **Multidisciplinary Health Professional Advisory Board (MAB)** will also be established during project year one. Membership will consist of multidisciplinary professionals from the surrounding practice community. During the first six months, the MAB will meet monthly to establish goals, define roles and responsibilities of members, and establish mechanisms to evaluate and prioritize needs and requests related to the health professional community. In subsequent years, the MAB will meet semi annually to provide input on barriers to clinical and translational research from the health provider perspective as well as to propose possible solutions. This group will also provide guidance on mechanisms to facilitate evidence-based practice and will provide specific feedback of the EBP pilot with regard to the progression of activities, specific process activities, and translational questions to be addressed. They will provide an annual evaluation of the progress and success of the EBP diffusion initiative. They will also contribute input to the identification of health professional needs with respect to participation in clinical research.*

A **Researcher Advisory Board (RAB)** consisting of investigators, coordinators, research associates, and students will be established during year. Efforts will be made to ensure representation across disciplines and specialties. This board will also meet monthly during the first six months to establish goals, define roles and responsibilities of members, and establish mechanisms to evaluate and prioritize needs and requests related to the researcher community. The RAB will then meet semi-annually to provide feedback on program activities and provide guidance for the modification to or addition of new program services.

### **Engagement of the Lay Community**

The lay community consists of the general public, patients undergoing care, members of occupational and business/professional groups, as well as foundations and organizations. Efforts directed toward the lay community will include each of these groups. The intent of the Community PARTners Program is to fully engage the community in an expanding and valued contribution to health and to enlist the community in development and utilization of clinical research. To this end, efforts will focus on educating the lay community, involving the lay community in the mentoring of investigators, promoting participation in clinical and translational research, and encouraging this community to play a role in the development of community-based research agendas.

### Educating the Lay Community.

The Community PARTners Program will draw upon existing resources to develop a comprehensive lay community educational program that is responsive to the needs of specific targeted communities and simultaneously provides general and specific information about clinical and translational research. New educational material will be developed when there is a documented need that cannot be met by existing resources. The CAB will guide the development of the educational campaign, which will serve to build a trusting relationship with the community by providing health-related services (e.g., health screenings, referrals for the uninsured) and responding to community needs for educational, research, and health screening services. This philosophy is consistent with recent trends in clinical research and increased public scrutiny that have underscored the importance of incorporating public education and outreach into the clinical research enterprise. The campaign will educate individuals about health-related issues that are relevant to them and their community, the impact of clinical and translational research on their lives, the value of research and the promotion of health and wellness. Several methods will be used, including culturally-sensitive seminars, health and wellness screenings, individual counseling by community-based health professionals (e.g., pharmacists, nurses, paramedics), interactive web-based resources, a community research registry, culturally-sensitive educational literature, advertising campaigns, public service announcements, community-based initiatives in partnership with public health organizations, schools, churches, service organizations, and foundations. University-based programs will be leveraged whenever possible. For example, the School of Medicine offers a "Mini-Medical School" for lay audiences that has been received favorably by the this community. Therefore, education pertaining to clinical and translational research will be incorporated into the Mini-Medical School curriculum. Dissemination methods for other programs will be guided by the characteristics and needs of the target population. The PARTners Program will also work closely with the CTSI Center for Clinical and Translational Informatics to provide web-based mechanisms of dissemination. A Community Outreach Speakers Bureau (COSB) will be established as a mechanism to educate and engage the public via the provision of services (e.g., health screenings and speakers) for public functions upon the request of community organizations. The project will be a collaborative effort of the CTSI and the UPMC Office of Grants, Contracts, and Intellectual Property and is compatible with the mission statements of the University of Pittsburgh and UPMC. Health promotion will be the primary objective of this outreach program, with promotion of participation in clinical research being a secondary objective. The COSB will include speakers from a variety of disciplines and specialties, and community organizations will define the topics for outreach activities.

### Mentoring Investigators and Trainees.

To promote lay community involvement in the mentoring of investigators and trainees, the PARTners Program will identify community organizations with an interest in serving as resources and service learning sites for investigators and trainees with an interest in community-based research. The Community PARTners Program will facilitate linkages for the investigators or trainees to work alongside these community members to develop a more in-depth awareness of specific communities. Benefits of this approach include enhanced relationships between investigators and service sites, greater understanding of community norms, increased responsiveness to community needs, stronger ties between the community and academia. This initiative will be evaluated from the perspective of the community organization and the mentee.

### Promoting Participation in Clinical and Translational Research.

The Community PARTners Program will engage the public and promote participation in clinical and translational research by providing services that are tailored to needs of the population in an accessible, community-based setting. A Community Continuity Screening Program will be established in collaboration with the CTSI Participant and Clinical Interactions Resources (PCIR) Core and the Urban League of Pittsburgh. This program will be housed in the new regional office of the Urban League, which will be located in a low income, primarily minority district within the city of Pittsburgh. This community home for the PARTners Program will facilitate access of the community to the university, and vice versa for the purposes of health screenings, health education, and participation in the clinical and translational research process. The Community Continuity Screening Program will be staffed by the Community-based Liaison, as described above. This concept has been endorsed by other community organizations (such as the Pittsburgh Theological Seminary) which have agreed to provide community homes for additional sites if evaluation results support expansion of the program.

The PARTners Program will also collaborate with the CTSI Novel Clinical and Translational Methodologies Core and the institutional public outreach campaign in the promotion of the system-wide registry of studies seeking subjects. Information about the registry will be disseminated at all educational and screening events facilitated by the PARTners Program. In addition, printed information on the registry (including the web address) will be distributed to all community partners, local libraries, and practice sites within the area. This information will include a registration form so that individuals not in the registry may join or sign up to receive a newsletter regarding studies that are being conducted at the University of Pittsburgh and affiliated institutions.

#### Setting Community-based Research Priorities.

Often the involvement of the lay communities is unidirectional. Communities are expected to value research, participate in studies as subjects, and advocate for research efforts while the ideas, the designs, the findings belong to the investigators. The intent of the Community PARTners Program is to expand upon this traditional approach to bring the lay community more fully into the research endeavor. The CAB will be utilized as a mechanism to involve the public in setting research priorities of interest to the community and contributing expertise to the research enterprise. Investigators planning to conduct studies within specific populations will be able to consult with the CAB. When appropriate, members of the CAB will facilitate the identification of subgroups that represent specific components of the community (e.g., elderly, parents, school teachers, unemployed, African American, Hispanic, Asian, Caucasian, Jewish, Muslim, disabled) to ascertain the health priorities of each that could help focus research efforts or facilitate recruitment. This will allow the CTSI to refer appropriate studies to the populations of interest as well as design communication for recruitment of populations that may have a lesser interest in specific questions. This approach will also enable us to identify how the community prefers to be approached, what the benefits to participation in studies would be and what sorts of incentives to participation could be ethically offered.

#### **Engagement of the Health Professional Community**

The health professional community is also made up of multiple subgroups, among them being physicians, nurses, pharmacists, dentists, physical therapists, occupational therapists, rehabilitation specialists, public health workers, and social workers. It also includes interdisciplinary groups within specialties; for example, psychiatry, endocrinology, cardiology, geriatrics, and pediatrics. Furthermore, the health professional community can be organized by setting in which care is delivered, such as acute care, long term care, home care, community settings, business settings, and public health. Just as different community groups are likely to have distinct cultures, values, and preferences, so too the various health care subgroups will have variations in culture, values, and preferences when it comes to clinical research. Efforts will be made to ensure representatives from each of these settings in program activities. The goal of this program component to develop a “research-informed multidisciplinary health professional community” that actively participates in (a) evidence-based practice that fosters the translation of research findings, (b) studies of participant recruitment, and (c) the conduct of clinical research. Several activities will be undertaken to accomplish those goals. To achieve this goal, the Community PARTners Program will focus on educating this community, involving the lay community in the mentoring of investigators, promoting participation in clinical and translational research, and encouraging this community to play a role in the development of community-based research agendas.

#### Educating the Health Professional Community.

In collaboration with the CTSI Center for Clinical and Translational Informatics, the Community PARTners Program will develop or adapt existing educational material and programs to a format that facilitates access by a geographically dispersed audience. Examples are web-based information, video conferencing and distance learning seminars for more outlying practices, and web casts. In addition, processes from the evidence-based practice pilot (described below) that have produced positive and satisfying outcomes will be translated to online educational programs for the health professional community to use for both new learning and for refreshment. These processes will serve to educate the community professionals, develop research partnerships, increase the value of clinical research to practice, and support the identification of strategies to translate research into practice.

#### Mentoring Investigators and Trainees.

The Community PARTners Program will involve multidisciplinary health professionals in the mentoring process by identifying community practitioners and practices with an interest in serving as a resource or service learning site. Interested investigators will be matched with community practitioners in the setting in

which their research is likely to take place to develop an understanding of the contributions and modifications that a setting may contribute to the procedures for carrying out clinical or translational research. Experiences would last from one day of shadowing a clinician or a patient to a week of integrating into the setting. It is anticipated that this sort of optional experience would serve to strengthen collaborations as well as offer an intensive informative exposure between clinician and investigator. To ensure a meaningful and constructive experience, this initiative will be evaluated from the perspective of the health professional and mentee.

### Setting Research Priorities.

*In an effort to engage the health professional community in setting research, priorities, the Multidisciplinary Health Professional Advisory Board will be charged with identifying research priorities and barriers to engagement in research. When appropriate, this advisory board will facilitate the identification of subgroups representing specific disciplines or settings. This will permit the PARTners Program to develop setting and discipline specific communication and to advise investigators on preferred practices in designing recruitment protocols and procedures for the conduct of research. It will also permit the matching of providers and investigators with similar research interests.*

### **Researcher Community**

Partnerships do not exist without adequate representation of all parties in the clinical and translational research arena. Therefore investigators and other members of the research team become critical elements in the development of partnerships to foster the expansion, efficiency, and utilization of clinical research. To that end the Community PARTners Program will undertake several initiatives for researchers. As previously noted, opportunities will be available for investigators to spend some brief periods of time in the lay and health professions communities for mentored learning experiences that are designed to foster an understanding of those communities. Other activities to be undertaken include education and the provision of service referrals.

### Educating the Researcher Community.

The PARTners Program will provide education to the research community by linking community members with existing programs. In addition, two new initiatives will be developed: a certificate program in Community Communication Skills and a Seminar Series on community based research.

The Community Communication Skills will be a formal certificate program that offered to investigators and trainees from the Schools of the Health Sciences to develop a “community and communication informed” investigator community. Development of this training program will be guided by input from the diverse elements of the three advisory boards. Curriculum will address communication skills, cultural and community sensitivity, and mechanisms to partner with lay and health provider communities. Continuing medical education credits and continuing education units will be available. Completion of this certificate program will be a prerequisite to investigator participation in the Community Outreach Speakers Bureau.

The Seminar Series will be offered in collaboration with the Research Education, training, and Career Development Core. Presentations will address issues such as community and population based research methods, evidence-based practice, intercultural communication, and ethical issues in community-based research. Continuing medical education credits and continuing education units will be available. Series lectures will be available via web-casts to ensure access by a geographically dispersed audience.

### Service Referrals for Researchers.

As previously described in the Administrative and Operational Foundation section, a centralized repository of university-based resources for community engagement will be established under the auspices of the Community PARTners Program. The CTSI-based Liaison will serve as a conduit to match investigator needs and requests with available resources. Requests might include assistance with public speaking, application of behavioral interventions, minority recruitment, use of technology in recruiting and following research subjects,

promoting adherence and retention in clinical research, working in rural communities, partnering with community service/business providers, population research methodologies, and other relevant areas. This expertise exists throughout the Schools of the Health Sciences. Rather than existing solely within a school, department, or division, the PARTners Program will coordinate efforts to make such expertise available to all investigators within the CTSI.

### **Pilot Project**

The Community PARTners Program will conduct a pilot project in evidence-based practice (EBP). This pilot will be based on the methods successfully employed by the School of Nursing's evidence based practice initiatives. A pilot **evidence based practice initiative** will be instituted in the first year of the PARTners Program. Practices within the set of community practices of the UPMC will be selected and an assessment of readiness and questions of interest will be conducted. This assessment will include a description of the practice, including the providers and the patient population seen, the resources within the practice to access the research literature, the experience and perceived skills of the health professionals and staff with research and EBP, the perception of barriers and benefits, as well as the perceived value of adopting EBP. Included will be a sociogram to determine the providers of influence within the community. EBP will be defined in two ways, the adoption of professional guidelines based upon research consensus, and the standard definition, that is, the individualization of care through the utilization of research findings, patient preferences, and practice capabilities. For the adoption of EBP, however, we will be utilizing the latter definition. Not only is this definition consistent with the concept of evidence based practice and the IOM guidelines for Health Professions Education<sup>17</sup> it is likely to address provider concerns that standard guidelines do not "fit" with individual patients. Survey results will be used to 1) identify a practice in which to initiate an EBP model; 2) identify barriers to research utilization among community providers that can be useful in planning translational research initiatives; and, 3) disseminate information on the barriers to and resources available for EBP in the practice community arena.

During the second year, the survey results will be used to identify and invite one or two practices invited to participate in a pilot program to implement EBP within multidisciplinary community practice. Practices will be selected which have an interdisciplinary model of care either through multidisciplinary professionals within the practice or through close collaboration in care with other discipline practices. The initial practice will be within the urban setting. Consistent with models of diffusion,<sup>3,11,18,19</sup> practice(s) will also be selected on the basis of their interest in adopting the model, their level of peer influence based upon the sociogram, and the availability of practice resources to move forward with the initiative. If the model is successful, as measured by the utilization of practices, satisfaction with the practices and the PARTners Program support for the project, and dissemination of the project to peers by the providers, practices with differing characteristics will be involved in the project, while outcomes outcome in the context of practice characteristics are consistently monitored. Reports on the outcomes of this model of diffusion will be disseminated, and the extent of participation in research studies following the EBP initiation will be monitored to determine whether the utilization of research may stimulate practitioners to partner in research efforts with investigators from the academic setting. As an incentive to the practices, support for dissemination activities (e.g. poster and/or slide presentations, collation of findings, tips and review of presentation skills) will be provided to the providers, with the expectation that individual providers would present to their local professional organizations and, potentially, to their national counterparts. The number of dissemination activities that are undertaken by the targeted group will be tracked and summarized annually.

The specific plan for implementation of the EBP model follows. A member of the Community PARTners staff will meet with the interdisciplinary practice partners initially on a weekly basis for one hour in the practice site at the close of office hours. Continuing education credits will be offered for these meetings. The staff will both educate and model the EBP process. Initially the practice partners will be guided to a clinical question of relevance to the majority of the practitioners and the identification of the domains of literature that may have relevance. The practice will be asked to appoint one staff person who will develop expertise in literature searching. It is expected that this person would perform literature searches for EBP as well as serve as a resource to others in the practice. During the week the staff member will be provided with literature searching strategies as an overtime activity paid for by Community PARTners. Such education and support is available through expert librarians in the Health Sciences Library. A "tool kit" for searching and integrating the findings of the search, including evidence to answer the clinical question and patient characteristics, is available within

the School of Nursing and will be available for use by the EBP project. Training activities will include a mentored search to bring evidence to the question that was raised by the practice partners.

The second meeting will consist of a review and discussion of the published evidence in the context of the characteristics of the patients in the practice. Discussions will focus on the quality of the evidence, the utility of the findings for patient subgroups, and proposed adaptations for use in the practice setting. Through this process the group will be mentored through the critical review of the literature and the generalizability of findings. Additionally, they will be guided through the process of adaptation to practice characteristics while remaining consistent with the findings reported in the literature. This discussion will continue with a third meeting, which will focus on the design of an implementation strategy. Attention will be given to the identification of targeted patients, training needs, if any, within the practice, identification of who within the practice is the most logical “interventionist”, and a plan for implementation. Thus, there will be three weekly meetings at the outset of the EBP dissemination activity. At the patient care implementation phase within the practice, Community PARTners staff will be available for consultation to the interventionist(s) over a one-month period of time. At the end of that implementation month, the assigned staff will meet with the practice group to identify successes, problems, and satisfaction with the EBP model within that practice. Problems will be addressed at subsequent meetings. Successes will be supported by monthly discussions with the practice for a period of six months, during which it is expected that new questions will be addressed, after which support will be gradually withdrawn and applied to a replication with appropriate modifications to a second practice partnership. Successful professionals/staff from the first site will be used to partner with the Community PARTners Program, with travel and time reimbursed, in the development of the second site. This model of peer dissemination will be evaluated and, if successful, will form the model for promotion of EBP within subsequent practice partnerships. By the third practice site, investigators will be invited to join in the educational effort both to bring their expertise to the program as well as to learn research translation strategies within the practice community. It is the intent to follow these initial programs with the development an application for funding to examine best practices for translation to practice, using an EBP model.

### **Evaluation**

Formative, process, and outcome evaluations of the Community PARTner Program activities will be conducted (see CTSI Evaluation and Tracking Plan). Development of program initiatives will be guided by a formative evaluation. Process and outcomes will be tracked and measured by collecting objective data. In addition, program participants will be surveyed to collect satisfaction data. Evaluation results will be reviewed by the program’s advisory boards and CTSI administration on a semi-annual and annual basis, respectively.

### **Timeline**

During the first six months of the program, efforts will be directed to start up activities. The first activity will be the formation of the advisory boards. Once these groups are in place, initial meetings will take place to review goals, outcomes to monitor, and processes planned. Establishment of a centralized repository of community engagement resources will also occur during the initial six months of the program. During the second six months, programs will be developed and necessary materials prepared.

The first offering of each of the Community PARTners Program initiatives will take place in the second year, beginning with the establishment of the lay community initiatives, followed by the EBP and health professional initiatives, and lastly the investigator initiatives. This will ensure that adequate attention can be paid to each initiative, with a view to integration across the program activities and the other cores of the CTSI. This sequence should ensure that adequate lay and health professions support is available before the investigators are brought into the partnership.

The third year will be focused upon repetition of programs along with evaluation, allowing for adjustments to be made with full community input before entering the fourth year. During the fourth year we will implement adjusted programs, again with evaluation and input from the various community boards. It is anticipated that preparation of the renewal application will utilize these experiences to drive and expand future activities.

### Transformational Elements

There are several transformational elements within the Community PARTners Program. First is an administrative and operational structure with representation from all stakeholders. This innovative structure will permit ongoing interaction with a multidirectional flow of communication among the critical elements in the community. The structure reinforces the value of each element of the broader community in a successful clinical and translational research enterprise. Second, the structure and activities address a neglected component of research education and dissemination by ensuring communities of laypersons, health practitioners, and investigators who have a better understanding of and ability to communicate with each other. Third is a structure that supports the diffusion and utilization of research through EBP and public communications initiatives. Fourth, the patient's experience of care delivery from multiple disciplines will be represented in the development and dissemination of critical knowledge and skills. Finally, a coordinated, centralized structure that is not dependent on funding cycles will enhance sustainability of the program. We believe that the infrastructure proposed for the Community PARTners Core will raise the value of clinical research, speed the dissemination of such research, and promote the partnerships so necessary for a successful clinical and translational research program in the interests of patient welfare.

**Literature Cited:**

1. Swazey JP, Fox RC. Remembering the “Golden Years” of Patient-Oriented Clinical Research: A Collective Conversation. *Perspect Biol Med*. 2004;47:487-504.
2. U.S. Department of Health and Human Services Public Health Service Grant Application (PHS 398) Instructions. Human Subjects Research Definitions. Available at: <http://grants.nih.gov/grants/funding/phs398/instructions2/phs398instructions.htm>. Accessed March 22, 2006.
3. Berwick DM. Disseminating Innovations in Health Care. *JAMA*. 2003;289:1969-1975.
4. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to Participation in Randomized Controlled Trials: A Systematic Review. *J Clin Epidemiol*. 1999;52:1143-1156.
5. Israel BA, Schulz AJ, Parker EA, Becker AB. Community-based Participatory Research: Policy Recommendations for Promoting a Partnership Approach in Health Research. *Educ Health*. 2001;14:182-197.
6. Baquet CR. Avoidable Disparities in Clinical Research Participation: Building Trust and Partnerships for Overcoming Health Professional and Community Barriers. Presentation at the *NIH Director's Council of Public Representatives (COPR) Workshop: Inviting Public Participation in Clinical Research: Building Trust through Partnerships*. NIH Bethesda, MD; October 26-27, 2004.
7. Calman N. Building Trust the Old-Fashioned Way: By Earning It. Presentation at the *NIH Director's Council of Public Representatives (COPR) Workshop: Inviting Public Participation in Clinical Research: Building Trust through Partnerships*. NIH Bethesda, MD; October 26-27, 2004.
8. Agency for Healthcare Research and Quality. Translating Research into Practice (TRIP)-II Fact Sheet. Available at: <http://www.ahrq.gov/research/trip2fac.pdf>. Accessed March 14, 2006.
9. Schuster MA, McGlynn EA, Brook RH. How Good is the Quality of Health Care in the United States? *Millbank Q*. 1998;76:517-563.
10. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud P-AC, Rubin HR. Why Don't Physicians Follow Clinical Practice Guidelines? A Framework for Improvement. *JAMA*. 1999;282:1458-1465.
11. Green LW. From research to “best practices” in other setting and populations. *Am J Health Behav*. 2001;25:165-178.
12. NIH Roadmap for Medical Research. Overview of the NIH Roadmap. Available at: <http://nihroadmap.nih.gov/overview.asp>. Accessed March 23, 2006.
13. NIH Director's Council of Public Representatives (COPR) Workshop: Inviting Public Participation in Clinical Research: Building Trust through Partnerships. NIH Bethesda, MD; October 26-27, 2004.
14. U.S. Census Bureau. 2004 American Community Survey, Allegheny County, Pennsylvania Fact Sheet. Available at: [http://www.achd.net/biostats/commprof.php](http://factfinder.census.gov/servlet/ACSSAFFacts?_event=&geo_id=05000US42003&_geoContext=01000US%7C04000US42%7C05000US42003&_street=&_county=Allegheny+County&_cityTown=Allegheny+County&_state=04000US42&_zip=&_lang=en&_sse=on&ActiveGeoDiv=geoSelect&_useEV=&pctxt=fph&pgsl=050&_submenuId=factsheet_o&ds_name=ACS_2004_SAFF&_ci_nbr=null&qr_name=null&reg=null%3Anull&_keyword=&_industry=.</a> Accessed March 22, 2006.</li><li>15. Allegheny County Health Department. Allegheny County Community Health Profiles. Available at: <a href=). Accessed March 8, 2006.
16. Healthy People 2010. Available at: <http://www.healthypeople.gov/>. Accessed March 1, 2006.



17. Greiner AC, Knebel E, eds. *Health Professionals Education: A Bridge to Quality*. Washington, D.C.: The National Academies Press; 2003.
18. Lavis JN, Robertson D, Woodside JM, McLeod CB, Abelson J, the Knowledge Transfer Study Group. How Can Research Organizations More Effectively Transfer Research Knowledge to Decision Makers. *Millbank Q*. 2003;81:221-228.
19. Rogers EM. *Diffusion of Innovations*. 4<sup>th</sup> ed. New York, NY: Free Press; 1995.

***Transforming Health Practice*****CTSI Catalyst Program: Developing New Therapeutics and Diagnostics**

Despite recent progress, development of more effective therapeutic agents and diagnostics has been frustratingly slow. Academic Health Centers (AHCs) are well suited for clinically relevant scientific discovery; however, once a target for therapeutic intervention or measure has been identified, AHCs are limited in their ability to focus a sufficient array of powerful resources on the development of needed quantities and clinically acceptable quality of optimal therapeutic agents<sup>1-5</sup>. Conversely, strengths in the pharmaceutical industry include large, flexible laboratories that can be focused on a single therapeutic goal and well-integrated systems that use million-compound libraries; high throughput screening systems; highly industrialized, computerized robotic assay systems; and teams of combinatorial chemists to create nanomolar leads for agonizing or inhibiting targets of choice. Those involved in large biotechnology companies develop biologic agents, gene therapies, and cellular therapies with substantial resources to advance novel therapies and diagnostic agents. Moving beyond proof of concept studies, international manufacturing and clinical teams are available within major pharmaceutical companies to manufacture and distribute therapeutic and diagnostic agents, to support multi-center clinical studies for evaluation of safety and efficacy, and for registration of agents and diagnostics of value to patients within AHCs<sup>5-8</sup>. AHCs continue to turn out promising ideas, but the handoff to industry is challenged by the disconnect between basic research findings and the desires of industry to in-license later stage compounds with clinically relevant proof-of-concept data in large animals or humans. Combined with the challenges of negotiating the intramural and extramural conflict of interest issues between academic laboratories and industrial partners, the chasm widens further.<sup>9-14</sup>.

The Clinical and Translational Science Institute (CTSI) recognizes the limitations of pursuing therapeutics/diagnostics [Rx/Dx] exclusively within the confines of an AHC such as the University of Pittsburgh, despite its broad strengths in biology and translational research and the presence of many creative scientists and skilled clinical investigators. At the same time, it is recognized that there are commerce-driven restrictions on the scope of research initiatives as well as increasing fiscal constraints within the pharmaceutical and biotechnology industries. Thus there is a compelling case for more effective partnering between AHCs and industry to maximize the impact of scientific discoveries on human health. True partnerships, as proposed in the CTSI Catalyst Program, require more than scientific aptitude. Partnering requires an arrangement through which both parties benefit; once established, partnerships require continuous communication and effort to ensure that performance goals are achieved. The CTSI Catalyst Program proposes to shift the locus of industry-academic relations from a PI-centered model to one in which the PI is part of an organized team assembled to initiate, plan, and execute large-scale partnerships with industry. Such efforts will expedite movement of basic biomedical discoveries through the pipeline, resulting in the production of diagnostics and therapeutics that are effectively translated into clinical practice. The CTSI Catalyst Program will seek proactive, strategic alliances with industry partners as exemplified by the CTSI Diamond/Intel Program (see CTSI Novel Clinical and Translational Methodologies Core). The Catalyst Program will establish 1) novel training programs for students, residents, fellows, and faculty designed to establish closer interactions with companies that are relevant to the broad goals of the CTSI and 2) an innovative program to stimulate development of projects in collaboration with industry.

The two following Specific Aims are proposed:

1. To promote training of health science students and faculty to advance understanding of the role of the partnership between academic health centers and industry in developing novel therapeutics and diagnostics.
2. To catalyze strategic and proactive engagement with select industry partners in the development of a commercial value chain around the AHC's most promising interventional strategies.

**BACKGROUND****Creation of New Knowledge.**

Historically, the academic training environment of biomedical scientists has promoted a value system that emphasizes the focused pursuit of new, and usually basic or fundamental, knowledge, while subtly discouraging perceived less intellectual research associated with translating new knowledge for the benefit of patients. The traditional academic value system has led to an avalanche of advances in understanding the biology of a wide variety of diseases, yet has been less supportive of the efficient translation of those ideas into life-enhancing/life-saving products. With the unprecedented expansion of federal dollars into academic

biomedical research over the past several decades, it was perhaps inevitable that the American public and the US Congress would eventually want to know what it was receiving for its investment in research in terms of new health-care products and services. Such translation requires academic-industry partnerships. The landscape of commercialization of new ideas is complex, including critical areas such as the protection of intellectual property, the use of translational techniques consistent with industry standards (such as GMP methods), and recognition of the need for relevant proof of concept data that minimizes commercial risks. Today's academic scientist must understand and support the creation of the commercial value chain that permits adoption of ideas by industry partners.

### **Creation of New Therapeutics/Diagnostics.**

With the passage of the Bayh-Dole Act in 1980, the US Congress took a significant step in addressing the issue of commercialization of intellectual property developed with government funding. The Bayh-Dole Act transfers exclusive control of many government-funded inventions to universities operating with federal contracts for the purpose of further development and commercialization. The contracting universities are permitted to exclusively or non-exclusively license the inventions to other parties. The initial response of many universities to the Bayh-Dole Act was to create offices of technology management (OTMs) to facilitate the licensing and commercialization of university-based intellectual property (IP). The OTMs provided a new mechanism for university professors to both protect their intellectual property and facilitate the development of products from their research efforts. However, the actual stream of ideas from the AHCs to the marketplace was not supported by a concomitant focus on the translation of basic science discoveries to products intended to treat patients. Despite their best efforts, OTMs are only a part of the commercial value chain required to move new discoveries from AHCs to the marketplace, where they can become products and improve society.

### **The University of Pittsburgh Schools of the Health Sciences Approach to Balance Value and Knowledge Creation.**

The University of Pittsburgh Schools of the Health Sciences have tried aggressively to meet the challenge of maximizing translational research with a proactive, multifaceted approach. First, and perhaps most importantly, the University has encouraged a paradigm-shift in the faculty mindset regarding technology commercialization and intellectual property. This paradigm-shift recognizes the role that AHCs play as stewards of public monies and promotes and rewards not only the creation of new knowledge but also the development and employment of that knowledge for the benefit of humankind. The University has developed programs that tangibly recognize the community of research scientists and inventors. For example, the Chancellor, Provost, and Senior Vice Chancellor for the Health Sciences (SVCHS) annually hold a campus-wide awards ceremony for University innovators. The importance of this recognition and support of academic value chain systems at the highest levels cannot be overstated. Another notable accomplishment that has transformed the University's translational environment is the remarkable effectiveness of the University's Office of Technology Management (OTM), in large part due to the leadership of Marc S. Malandro, Ph.D. Because of Dr. Malandro's scientific training and experience in the commercial biotechnology sector, including founding of start-up companies, he understands technology transfer issues from both the academic and industry perspectives and can thus identify the appropriate middle-ground for win-win technology transfer. The OTM takes a hands-on approach, with continual and regular faculty contact, rapid and timely analysis of invention disclosures, access to top quality legal services, and careful handling of sensitive licensing agreements. In addition, the OTM has established numerous funding sources for internally supporting translational science that provides proof of concept data. Funding programs include State of Pennsylvania economic development funds as well as internal discretionary funds provided by the Provost and the SVCHS. These small but critical dollars can be used to support the development of scientific data crucial to the establishment of the commercial value chain.

### **The University's Office of Enterprise Development (OED), Health Sciences.**

In 2000, the premise was conceived for what is today the University of Pittsburgh Office of Enterprise Development, Health Sciences. Born out of the University of Pittsburgh Cancer Institute, the OED rapidly became highly successful, as evidenced by a progressively increasing number of cancer research faculty participating in the OED educational sessions on entrepreneurship, invention disclosures, startup companies, and licensing deals with industry. Accordingly, in 2004, the SVCHS broadened the mission of the OED to include entrepreneurial and commercialization initiatives across all of the schools of the health sciences. The OED is innovative and highly complementary to the OTM. The OED recognizes the significant complexity of translating medical technologies and, as such, it educates and assists faculty from across a wide range of disciplines in entrepreneurship, technology transfer, and conflict of interest issues. The OED helps faculty members who have brought their research to the next level—where moving it forward means moving it out of the University and into the hands of a business partner. The OED's founding Director, Carolyn Green,

continues to build this multi-pronged program that supports faculty members from idea through commercialization, as the commercial value chain is created and leveraged. Since inception just five years ago, the OED has now become an integral part of the University of Pittsburgh Schools of the Health Sciences, educating many faculty in the processes associated with technology transfer and commercialization, growing new companies, and spawning new collaborations with industry partners in areas as diverse as cancer, tissue engineering, diagnostics, obesity drugs, and medical devices. The key to OED's success is its professional team composed of business-savvy scientists implementing a model for a different kind of technology transfer—one that is centered on the active involvement of the inventor and that focuses on developing a unique value creation plan for each discovery, aimed at moving it from the benchtop to the patient. The OED facilitates interactions with the OTM and with business and industry partners, which are proactively engaged by the OED team. OED is a central link bringing the University of Pittsburgh's world-class researchers together with the life sciences business community. By connecting University scientists and inventors with industry professionals, OED acts as a catalyst, stimulating academic-industry collaborations. OED also assists in the development of new life sciences start-up companies in the Pittsburgh region. Together, the OTM and the OED ranked 6<sup>th</sup> in most new start up companies for 2004 (AUTM survey 2004)

In 2005, Mitchell P. Fink, M.D. was made Associate Vice-Chancellor for Translational Research and Commercialization, as well as OED Medical Director. Dr. Fink also serves as a critical link with UPMC Strategic Business Initiatives, a venture-capital style investment arm of UPMC. Dr. Fink is an accomplished physician-scientist as well as entrepreneur, having successfully translated drugs in the area of critical care medicine. He provides much-needed strategic planning advice for the development of value creation plans.

#### **Example of the Development of New Diagnostics/Therapeutics at the University of Pittsburgh: Small Molecule Drug Discovery.**

The infrastructure for small molecule drug discovery and development at the University of Pittsburgh continues to evolve rapidly and profoundly. As part of the NIH's Roadmap initiative, the agency has awarded grants to nine institutions, establishing a Molecular Libraries Screening Centers Network that uses high-throughput screening techniques to identify small molecules that have the potential to make an impact on various diseases. Through this initiative, the University Of Pittsburgh School Of Medicine received \$9 million from NIH to establish the University of Pittsburgh Molecular Libraries Screening Center (UP-MLSC). John Lazo, Ph.D. Allegheny Foundation Professor of Pharmacology is principal investigator of the UP-MLSC. This facility will occupy 21,000 ft<sup>2</sup> on the 9<sup>th</sup> and 10<sup>th</sup> floors of the University's newly opened Biological Science Tower 3, triple the space previously allotted for drug discovery research at the University of Pittsburgh. The UP-MLSC is exploiting the University's strength in interdisciplinary pharmacology, chemistry, and cell biology research to support academic small molecule interrogation using high-throughput screening techniques. The University is one of the few academic centers that has this capability, due, in part, to the utilization of the Celloomics (Pittsburgh, PA) ArrayScan VTI. This instrument allows sub-cellular localization of pharmacologically attractive targets. Most drugs function to inhibit an enzyme, but there is also an opportunity to examine compounds that function by displacing or replacing a pharmacologically important target to the right subcellular compartment. Doing this type of research in an academic setting is highly unusual, and the UP-MLSC is using instrumentation that was designed for big pharma and exploiting it by focusing efforts almost exclusively on rare and orphan diseases, a sector less well-studied by industry. The goals of this interdisciplinary research are to foster collaborations among translational and clinical scientists to establish research programs in rare and orphan diseases and to direct assets toward taking a lead compound sufficiently toward development to attract the needed interest of a commercial entity. The UP-MLSC is also developing new high-throughput assays that can be shared to aid in screening the approximately 100,000 compounds that reside in the Molecular Libraries Small Molecule Repository, located in San Francisco at Discovery Partners International. The UP-MLSC is in the process of launching drug discovery efforts in zebrafish to capitalize on the University's 100,000 tank capacity, the largest in US academia.

#### **Example of the Development of New Diagnostics/Therapeutics at the University of Pittsburgh: Combinatorial Chemistry Center.**

The Combinatorial Chemistry Center resides in the Department of Chemistry. It was founded in 1998, with institutional support from UPMC and the University of Pittsburgh Cancer Institute. In fall 2002, the center was expanded into the Center for Chemical Methodologies and Library Development (UPCMLD) and received a NIGMS grant to build one of the nation's first Centers of Excellence in Chemical Methods and Library Development. The main goal of the UPCMLD is to generate novel chemical libraries based on original research carried out in the areas of synthesis and analysis of novel peptide mimetics, the combination of solid phase and fluororous phase organic synthesis, and the development and implementation of fluoropolymer-based microreactors. The UPCMLS applies diverging strategies to assemble architecturally unique scaffolds using

transition metal catalysis, to develop new separation technologies using fluororous phase synthesis strategies, to design and develop microreactors for nano-scale highly parallel organic synthesis, and to discover new chiral stationary phases for HPLC. The Diversity-Oriented Synthesis Core validates library procedures and prepares and distributes the UPCMLD Library.

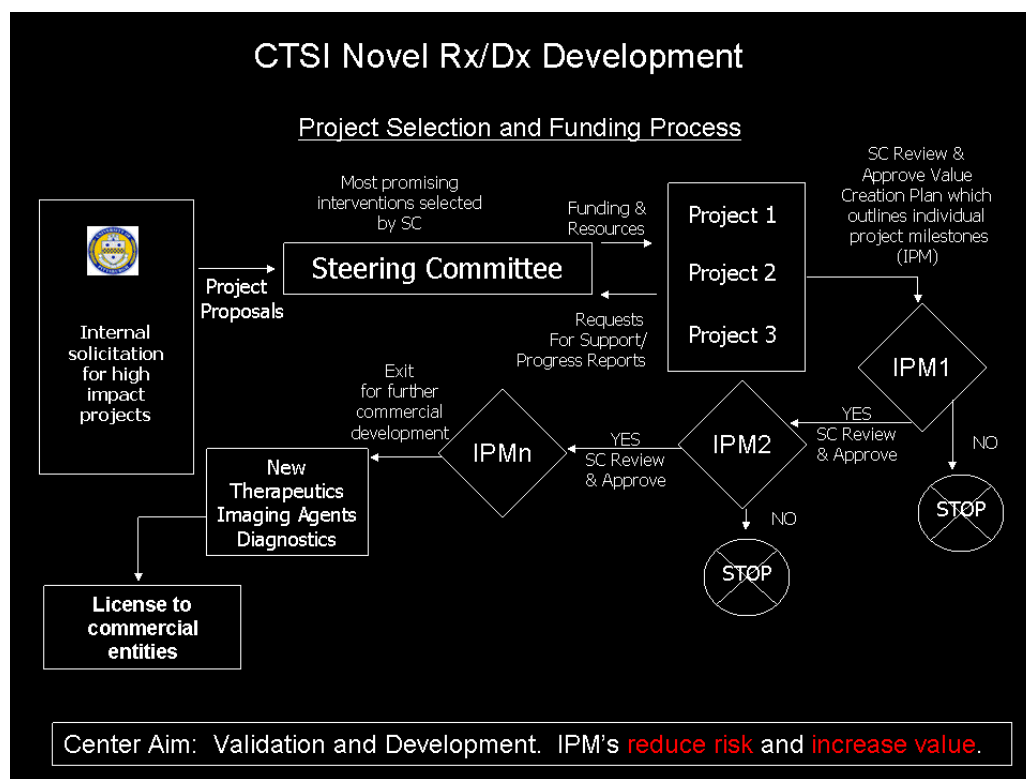
### **Example of the Development of New Diagnostics/Therapeutics at the University of Pittsburgh: Protein Therapeutics/Biotherapy.**

Michael Lotze, M.D. (Core Director, CTSI Catalyst Program) helped develop T-cell growth factor/Interleukin 2 as a therapeutic strategy, ushering it from a biologic activity through its earliest clinical testing through to its marketing as a successful biopharmaceutical and recombinant protein as the first approved therapy for patients with metastatic renal cancer and later in patients with metastatic melanoma. Subsequently he has been creatively involved in developing cytokine therapeutics including IL-4, IL-12, and IL-18 at both the University of Pittsburgh and GlaxoSmithKline. Since the advent of additional NK cell-based therapeutics, the Lotze group has championed the US adoptive transfer of T-cells, dendritic cells and of gene therapies for cancer therapeutics.

## **CORE DESIGN and METHODS**

### **CTSI Catalyst Program for Development of Novel Therapeutics/Diagnostics [Rx/Dx]**

The University of Pittsburgh schools of the health sciences have particular strengths in molecular and cellular biology, gene-environmental interactions, molecular therapeutics and drug discovery, immunology, and biological therapy. To complement these assets, the CTSI will liaise with the OED and the OTM, and their industry partners, to establish a formal process for selection, funding, and promotion to industry of the most promising therapeutic and diagnostic leads (Figure 1). With the broad-based and extensive research programs at the University, and the existence of a highly interactive and collaborative interdisciplinary translational research environment under the leadership of Dr. Steven Reis, who serves as both the CTSI PI and the Associate Vice Chancellor for Clinical Research, Health Sciences, the CTSI will quickly and efficiently mobilize the appropriate multidisciplinary teams, facilities, and equipment to advance projects toward commercialization as milestones are met or altered. The goal will be to mature the proposed interventional



IPM=Individual Project Milestone

product or biomarker to a commercially viable product while simultaneously reducing the risk and increasing value for the investigator by eliminating unknowns and providing critical information regarding the viability of the proposed product. Throughout the process, the CTSI will utilize its close partnership with the OED and the OTM to identify suitable partners for interaction and to nurture relationships between investigators and industry. These partners are well positioned to proactively engage prominent industry partners who bring strengths in developing novel technologies.

The University of Pittsburgh CTSI will provide training and expertise in, and opportunities for, the development and translation of novel therapeutics and diagnostics through the creation of a commercial value chain. First, the CTSI will develop new diagnostics and therapeutics through the efforts of several CTSI Cores (e.g., Novel Clinical and Translational Methodologies; Translational Technologies and Resources). Second, the

CTSI Catalyst Program will advance the development of these discoveries by 1) providing trainees with the fundamental knowledge required to build and evaluate Value Creation Plans around any health science discovery, including intellectual property protection, regulatory processes, and market evaluation, and 2) catalyzing and providing seed funding for investigator–industry partnerships.

**Aim I. To promote training of students and faculty in the health sciences to advance understanding of the role of the partnership between academic health centers and industry in developing novel therapeutics and diagnostics.**

**Identification of Students.**

The CTSI will engage students, residents, postdoctoral fellows, and faculty from throughout the health sciences schools, centers, and institutes to interact through training grants and novel programs with industry partners to advance their knowledge and understanding of product development strategies. The program will have two tiers, one for a group of four carefully chosen scholars to engage in a year-long *intensive experience with an industry partner* and a *broad-based educational tier* for other interested students, residents, postdoctoral fellows, and faculty.

The scholars who participate in the intensive industry collaboration experience will be drawn from the graduate programs of the health sciences schools, ideally during the first year after they complete most of their required didactic material. A particular emphasis will be placed on identifying medical students who are interested in participating in this program as the foundation of the Scholarly Project that all medical students are required to complete. The four scholars selected for the industry-intensive experience will receive 50 percent of tuition, fees, stipend, and fringe benefits through the CTSI. Students will be selected in a staggered fashion and will be guaranteed two years of support. Expansion of the program beyond the complement of four students budgeted in this proposal will require both clear success, as exemplified by the student's required final project, and new resources from additional partnering arrangements, philanthropy, and/or federal sources.

The programs that will be established for the broader academic community will:

1. Educate health sciences students, resident, fellows, and faculty on the principles of intellectual property and federal legislation governing its development with academic institutions, and
2. Develop training programs with students within the K12/K30 programs, as well as in other graduate medical and doctoral programs, which enable interactions with biotechnology and pharmaceutical firms

To comply with both the scope and mission of this program, the CTSI, in partnership with the OED, will create the infrastructure and culture whereby students, residents, fellows, and faculty are informed about and engaged in the process of intellectual property creation and management and the process of partnering effectively with companies to advance novel diagnostics, therapeutic agents, devices, and services. This novel program will 1) provide a context and setting for education in coupling value and knowledge creation; 2) promote the recruitment, training, advancement, and retention of new clinical and translational investigators who are also informed in managed corporate alliances; 3) provide a core curriculum in Project Management in Collaborative Projects spanning material transfer agreements, sponsored research agreements, clinical trial agreements, and related mechanisms; 4) engage master's and doctoral students in the T32 program; and 5) introduce business, legal, and statutory elements into the curriculum of the highly successful K12 Program.

**Selection of Students.**

The CTSI will be used as an umbrella organization to promote interactions among faculty, fellows, and students at all levels (see CTSI Research Education, Training, and Career Development Core) by introducing OED programs earlier and earlier in the educational process. The CTSI Catalyst Program will also develop coursework appropriate at each level and related to the primary areas of investigation. Ongoing assessment will track the number of courses offered, as well as the number of applicants and attendees. As a starting point, the OED course, "From Benchtop to Bedside" will be made available to all faculty and to select students, residents, and postdoctoral fellows.

Members of the Steering Committee that will select students from an applicant pool of graduate or medical student researchers will include those who helped initiate and draft this section of the CTSI: Michael T. Lotze, MD (Director Strategic Partnerships UPCI, MMI, STI, MIRM) and Carolyn Green (OED, Co-Chair), Andrew Remes, PhD (OED), Mitchell Fink, MD (Associate Vice Chancellor for Translational Research and

Commercialization), Ronald B. Herberman, MD (Director University of Pittsburgh Cancer Institute and Associate Vice Chancellor for Cancer Research), Loren Roth, MD, MPH (Associate Senior Vice Chancellor for the Health Sciences, University of Pittsburgh and Senior Vice President, Quality Care and Chief Medical Officer, UPMC), Edward D. Jackson, PhD (Dept. Pharmacology), Harvey Borevetz, PhD (Chairman of Bioengineering), Marc Malandro, PhD (Director, Office of Technology Management), Allen DiPalma and Kelly Downing (Office of Research), Joseph Glorioso, PhD (Chair of Molecular Genetics and Biochemistry and Director, Molecular Medicine Institute), Fadi Lakkis, MD (Scientific Director, Starzl Transplantation Institute), and Alan Russell, PhD (Director, McGowan Institute for Regenerative Medicine). This group will design and implement the process of student identification and selection and provide a means for reflecting on the successes of the program. These persons will also make up the Steering Committee as identified in Aim II.

### Measures of Success.

Feedback from participants in the form of evaluations; number of funded investigations with student participation, and satisfaction on the part of the industrial partner will be measured. Funded programs engaging students within commercial partnerships is a long-term goal. Participation in courses and types of material being developed by students, residents, fellows, and faculty and careful examination of feedback will be used to make material relevant. Feedback will also be sought from commercial partners as to the merit of efforts from their perspective, as compared to similar institutions. Four students will be identified and funded by the end of two years; the program will be cautiously expanded to 8-12 funded students through this program by the end of five years.

### **Aim II. To catalyze strategic and proactive engagement with select industry partners in the development of a commercial value chain around the most promising interventional strategies.**

The Office of Enterprise Development (OED) acts as a resource for health sciences faculty to encourage and facilitate pursuit of entrepreneurship and interactions with industry. OED management models that will serve CTSI investigators are outlined in Table 1.

**Table 1. Office of Enterprise Development and Office of Technology Management Models for Industry Collaborations around novel Rx and Dx**

<b>“Research Tools” Collaborations</b>	<b>Multi-disciplinary research teams organized around a partner’s interest</b>	<b>Collaborations involving Drugs, Diagnostics, Medical Devices</b>
<p><i>Purpose:</i> To develop <b>new research tools to be used broadly</b> in the pursuit of scientific discovery. Project may include multiple research partners aiming to address fundamental science issues.</p> <p><i>Nature of the partnership:</i> A group of external partners may provide funding and/or personnel to the consortia; work may be done in any partner location.</p> <p><i>Contractual method:</i> Consortia members would enter into a U54 type mechanism with membership fees used to support the research work; new intellectual property developed by the consortia are shared among the participants, and are also available for licensing to non-participants at a fee.</p> <p><i>Expected outcomes:</i> New research</p>	<p><i>Purpose:</i> Organize a team of investigators from across disciplines with a focus on <b>discovery</b> of novel interventions in a given area of medicine (defined scope of the research project)</p> <p><i>Nature of partnership:</i> A single external partner provides funding and/or personnel to the research team; work is done primarily in University facilities.</p> <p><i>Contractual method:</i> For preclinical research, a university SRA, with sponsoring entity, to receive a time limited right of first offer on new intellectual property developed under the scope. For clinical research, a Clinical Trials agreement, with the sponsoring entity receiving a right of first offer to any new intellectual property developed, but with strong safeguards for pre-</p>	<p><i>Purpose:</i> To further <b>develop a pre-existing university discovery</b>; goal is to perform proof of concept work to establish viability of discovery as having the potential to become a commercially available drug, device or diagnostic test, likely requiring approval of the FDA.</p> <p><i>Nature of the partnership:</i> A single external partner identifies a specific pre-existing university discovery for development; partner agrees to fund further development inside the university in exchange for certain rights.</p> <p><i>Contractual method:</i> University and partner enter into an option agreement and a sponsored research agreement. The work will be performed by University personnel. Partner would be afforded the right of first offer on newly developed inventions</p>

tools that can be broadly licensed for use across academia and industry	existing intellectual property of both parties.  <i>Expected outcome:</i> New discoveries aimed at improving human health.	during the period of the research.  <i>Expected outcomes:</i> Translation of research ideas into products under development by pharma and biotech partners.
<i>Examples:</i>  Intel-Diamond  Pittsburgh Digital Greenhouse	<i>Examples:</i>  Contemplated with Lilly, Invitrogen, GSK, Amgen, TetraLogic, and others	<i>Examples:</i>  Pitt has already done this successfully with many companies such as StageMark, Cellumen, etc.

The OED's models incorporate the development of Value Creation Plans, which are utilized to promote the development of novel interventions. Using the CTSI Pilot and Collaborative Studies Core, the OED will promote regular, broad solicitations to the clinical and translational science community for lead candidate development proposals that will be funded by the CTSI Catalyst Program. A Steering Committee, named in Aim I, will review and prioritize proposals for the following attributes:

- Scientific Merit
- Intellectual property status
- Potential clinical impact of discovery on a patient population (if successful in translating)
- Potential for adoption by commercial partner for further development
- Merit of the proposed Value Creation Plan, or if not given, the potential to successfully develop a viable Value Creation Plan, including go/no-go individual project milestones (IPM)

As noted, the CTSI will fund promising pilot projects that have high potential for future development into commercial projects. CTSI funds will be leveraged as a result of the ongoing, stable, and productive collaboration between the University and UPMC. UPMC is a potential funding source for development of promising Rx and Dx and has the ability to invest in meritorious activities and strategic business initiatives. UPMC has and can also provide important proof of concept transitions crucial to the establishment of partnerships with established commercial pharmaceutical and biotechnology entities. Pharmaceutical firms such as Eli Lilly, TetraLogics, Amgen, Sanofi, among others, as well as the Pittsburgh Life Sciences Greenhouse (a local economic development agency that incubates and funds start-up companies in the life sciences), have been identified as initial corporate partners. These groups are particularly well suited to pursue the basic development, translation, and clinical implementation of Rx/Dx based on small molecule drug discovery, biological therapeutics, molecular genetic and cellular therapeutics, and diagnostics.

Funded pilot projects will demonstrate: 1) the ability of University of Pittsburgh scientists and clinicians to conduct research aimed at significantly improved timelines and milestones to promote translational research; and 2) the availability of appropriate resources derived from both the CTSI and its partners. Both the expertise and interests of CTSI investigators and resources available to support their work should be relevant to the application envisioned by the partner. Research proposals will also harbor the potential to provide the basis for interventions applicable to a much broader spectrum of disease and substantial unmet medical need. When



combined with the expertise of UPMC, pharmaceutical firms such as Lilly and TetraLogic, and the many PLSG member companies, the CTSI will effectively focus on rapid discovery, preclinical development, and translation to important clinical applications. In addition to strong disease site-focused translational research programs, the CTSI has multiple critical research programs/core facilities that will be central for support of the CTSI's efforts to enhance innovation and efficiency, rapidly developing Rx/Dx.

### **Research Project Solicitations, Review, Termination and Management.**

The conceptual framework for managing each individual research project is shown above in Figure 1. This figure highlights the ability of the Steering Committee to identify work-teams, develop new projects, and manage project renewals based on setting and evaluating individual project milestones. The initial research projects will be selected by the Steering Committee (see above) from proposals received in response to an initial solicitation, which will be sent to faculty. Upon funding of the application, the Steering Committee will incorporate the reviewers' comments into the selection, design, milestones and evaluation of specific projects that have been proposed. All of this will be the basis for the written Value Creation Plan. The Value Creation Plan may include modifications of specific aims, methodology, milestones, evaluation criteria, and potentially, substitution of projects if warranted. As a funded CTSI project, the PI will have access to all CTSI core facilities as well as to a uniquely developed team of experts who compose the Value Creation Plan team. Given the nature of drug discovery and development, it is likely that some projects will fail to meet specified milestones for continued preclinical development, in which case any such project will be promptly terminated and alternate projects will then be considered for utilization of the newly available resources. As the opportunity for funding new projects occurs, a request for proposals (RFP) will be issued according to the described procedures.

### **Requirements of Individual Projects.**

Any faculty member in good standing may submit a project proposal in response to a request for proposals (RFP). The research must be performed at the University or by a bona-fide subcontractor to the University. Accordingly, the CTSI will require that the principal investigator be employed by the University of Pittsburgh (or affiliated institutions like Carnegie Mellon University). The Steering Committee may choose to focus an RFP on a particular clinical or scientific area; however, it is envisioned that the criteria for all RFPs will include, at a minimum:

- Interventional approach to unmet clinical needs or potentially useful biomarker to predict and/or assess response to interventions
- Direction toward a disease with interest from faculty/students at the University of Pittsburgh Schools of the Health Sciences
- Work plan that can be carried out by a PI located at, and in the facilities of, the University of Pittsburgh School of the Health Sciences or by a bona-fide subcontractor to the University
- Expectation that an acceptable, proof-of-concept milestone can be achieved within 6-12 months from the time of acceptance
- Expectation that continued funding depends on timely progress and successful achievement of milestones, as defined by the Steering Committee or its designee

The Steering Committee shall develop a topical list of special interests or needs to which proposals shall be directed. This topical list may change from cycle to cycle. Proposals may also be opportunistically accepted outside of this list if deemed highly innovative or promising. Since it is anticipated that at least one of the initial projects will fail to meet individual project milestones and be terminated within or after one year, RFPs will be generated and distributed at least once per year, so that well developed, high priority projects will be ready for implementation as soon as funds become available. The RFP format will be specified by the Director of the CTSI Pilot and Collaborative Studies Core and distributed widely by the CTSI.

### **Proposal Review.**

The Steering Committee will be responsible for the technical and business review of all proposals. Steering Committee members may seek additional input from within their own departments on specific proposals as long as confidentiality requirements are maintained. At the Steering Committee meeting, members will discuss and rank the submitted proposals according to the following criteria:

- Significance and fit with CTSI Catalyst Program mission, goals and objectives, and its policies and procedures
- Probability of developing/influencing new clinical applications
- Scientific merit
- Innovation in approach and importance of the problem

- Qualifications of PI, team, and environment

Numeric scores will be assigned to each project by each Steering Committee member and compiled by the CTSI Catalyst Program Director. The Steering Committee will then allocate available funds among the highest scoring projects. It is anticipated that projects will initially be funded for a period of six-twelve months, during which they will be required to demonstrate achievement of necessary proof-of-concept milestones. Milestones will be required to be proposed by the applicant within the application mechanism, but will be subject to revision by the Steering Committee, to ensure that the proposed milestones are sufficiently specific and are most likely to advance the technology from an applied research perspective. At the time of each individual project milestone and no less frequently than yearly intervals, applicants will report to the Steering Committee on the results achieved during the previous funding period, particularly in relation to the particular individual project milestones. If awardees seek a renewal of funding, they will be required to update their proposal with Phase 2 milestones that will be reviewed by the Steering Committee as described above.

**Project Monitoring and Reporting.**

The CTSI Catalyst Program Director will appoint an individual from the Steering Committee to monitor research progress on funded projects relative to proposed technical objectives, as well as related project outcomes. Such progress will be summarized and distributed to the Steering Committee members semiannually. Individual project milestones are aligned with (but not necessarily identical to) technical objectives and should be key decision points in evaluating the preclinical development of new interventions. The Steering Committee will review individual project milestone status in detail on each funded project at its semiannual meetings.

**Project Termination.**

Projects not meeting technical milestones, or judged not to be clinically promising, may be terminated immediately by the Steering Committee at any time. Particular attention will be focused on individual project continuations at each semiannual Steering Committee meeting. Termination will require a two-thirds (2/3) vote of the Steering Committee members. The CTSI Catalyst Program Director will then be responsible for communicating the decision to the research team and working out a process for timely redeployment of the involved faculty and staff. Funds from the termination of a project may be 1) shifted to other ongoing projects, or 2) be used to initiate a new project, subject to the approval of two-thirds (2/3) of the Steering Committee.

**Literature Cited:**

1. Coleman DL, Kazdin AE, Miller LA, Morrow JS, Udelsman R. Guidelines for interactions between clinical faculty and the pharmaceutical industry: One medical school's approach. *Acad Med*. 2006;81:154-60.
  2. Brennan TA, Rothman DJ, Blank L, Blumenthal D, Chimonas SC, Cohen JJ, Goldman J, Kassirer JP, Kimball H, Naughton J, Smelser N. Health industry practices that create conflicts of interest: A policy proposal for academic medical centers. *JAMA*. 2006;295:429-33.
  3. Cripe TP, Thomson B, Boat TF, Williams DA. Promoting translational research in academic health centers: Navigating the "roadmap". *Acad Med*. 2005;80:1012-8.
  4. Chin-Dusting J, Mizrahi J, Jennings G, Fitzgerald D. Outlook: Finding improved medicines: The role of academic-industrial collaboration. *Nat Rev Drug Discov*. 2005;4:891-7.
  5. Cohen JJ, Siegel EK. Academic medical centers and medical research: The challenges ahead. *JAMA*. 2005 ;294:1367-72.
  6. Science-Based Solutions to Obesity: What are the Roles of Academia, Government, Industry, and Health Care? Proceedings of a symposium, Boston, Massachusetts, USA, March 10-11, 2004 and Anaheim, California, USA, October 2, 2004. *Am J Clin Nutr*. 2005;82:207S-273S.
  7. Topol EJ, Blumenthal D. Physicians and the investment industry. *JAMA*. 2005;293:2654-7.
  8. Mello MM, Clarridge BR, Studdert DM. Academic medical centers' standards for clinical-trial agreements with industry. *N Engl J Med*. 2005;352:2202-10.
  9. Korn D, Ehringhaus SH. NIH conflicts rules are not right for universities. *Nature*. 2005;434:821.
  10. Kimmelman J. Valuing risk: The ethical review of clinical trial safety. *Kennedy Inst Ethics J*. 2004;14:369-93.
  11. Kesselheim AS, Avorn J. University-based science and biotechnology products: Defining the boundaries of intellectual property. *JAMA*. 2005;293:850-4.
  12. Whitcomb ME. Academic health centers: Sustaining the vision. *Acad Med*. 2004;79:1015-6.
  13. Garber AM. Corporate treatment for the ills of academic medicine. *N Engl J Med*. 2004;351:1601-3.
- Steinbrook R. Conflicts of interest at the NIH--resolving the problem. *NE*

**CTSI EVALUATION AND TRACKING PLAN**

Funded through the Roadmap initiative, we are developing the University of Pittsburgh Clinical and Translational Science Institute (CTSI) to spur innovation in conducting clinical and translational research using a multidisciplinary, collaborative, team approach. Consistent with the NIH's Roadmap Initiative, the CTSI is exploring ways to improve the progress of research, re-engineer the clinical research workforce, and ensure that scientific discoveries move from the laboratory to the bedside. Unique elements of this program include the use of individualized training developed for each clinical and translational research scholar, support for researchers to work in multidisciplinary teams, and services for clinical and translational researchers to remove barriers frequently experienced in conducting this type of research.

Given the uniqueness of this program and the extent to which it will transform the University of Pittsburgh and its scientists, research, and health practice, we are committed to conducting formative and summative evaluations so that we can identify useful services for investigators and programs that need to be improved. The primary aim of our evaluation is to identify ways to improve the CTSI (Formative evaluation). Our secondary aim is to measure the impact of the CTSI on clinical and translational research at the University of Pittsburgh (Summative evaluation). These aims will assess the administrative and scientific functioning of the CTSI as well as its accomplishments. Data on CTSI performance will serve to inform ways in which the CTSI can be enhanced to improve its mission, redistribute resources more equitably, and identify which Cores are under-utilized or inappropriately used. Through our systematic measurement of performance, we will not only assess the accomplishments of the CTSI, but our evaluation will also inform us as to what aspects of the CTSI are more effective than others, enabling us to make adjustments as needed to the Institute.

Importantly, the evaluation will incorporate both quantitative and qualitative components. Qualitative data collection and analyses are especially important in novel and complex undertakings that involve a range of new structures and processes, the development of innovative tools, and a reorganization of the ways in which people work together. Understanding what works, what does not work, and why is critical not only for improving the operations of a single CTSI, but for informing the overall translational research enterprise. The qualitative component of our evaluation will be conducted independently by RAND Corporation analysts who are not directly involved in the activities of the University of Pittsburgh CTSI, thus ensuring the complete objectivity of the findings. In addition to supplementing the findings from the more formal quantitative evaluation, RAND also will provide external advice to the Core Evaluation Team regarding the planning of a more summative longitudinal evaluation.

The CTSI Evaluation Core will be directed by Doris Rubio, PhD, who has a strong background in evaluation, leads the evaluation of the existing Roadmap K12 at the University of Pittsburgh, and serves as the chair of the Evaluation Liaisons for the 12 NIH Roadmap K12 institutions. She brings experience and expertise in developing and implementing the evaluation plan for the CTSI. Our partnership with the RAND Corporation, brings additional expertise in evaluation and qualitative research. RAND has extensive experience in formative and process evaluations that involve primary data collection from stakeholders including administrative leaders, clinician researchers, clinicians who might participate in research, and clinicians engaged with special populations such as those with high-prevalence diseases (hypertension, diabetes, coronary disease, depression), middle-prevalence conditions (breast, colorectal, lung, prostate cancer), and low-prevalence diseases (rheumatoid arthritis).

We are using a logic model approach for our evaluation. While other models exist for evaluation (e.g., logical framework, cluster evaluation, and case study), the logic model offers the best approach for tracking measures within programs over time and monitoring changes in performance for different comparison groups. The logic model offers flexibility to adapt the evaluation strategy as the activities and/or outcomes change. In creating a transformative Institute, we anticipate that adjustments will need to be made. The logic model enables us to reflect those changes and yield useful data without compromising the overall evaluation strategy.

In order to create our evaluation plan, we developed a logic model for each CTSI Core, as well as the overall CTSI structure. From the evaluation plans, we identified variables to be measured and how they would be measured. Four main categories for measures are baseline characteristics or resources, process, short term outcomes (3 -5 years) and long term outcomes (10+ years). The baseline characteristics indicate what resources are present at the time of implementing the program. By measuring the process variables, we are able to know the extent to which the program is functioning as it was designed. These variables will enable

us to make changes where needed to such areas as: resource allocation; program Directors; or services offered. The outcomes provide an indication of the extent to which the CTSI achieved its aims and has an impact on clinical and translational research.

The evaluation plan for the CTSI is described as follows. First, we will describe our self-evaluation plan for creating the CTSI. Second, we will present the evaluation for each of the key functions (CTSI Cores), as described in the context of the transformative goals of the CTSI. In describing the evaluation for each Core, we will begin by identifying their aims and objectives. We will then discuss how the objectives will be evaluated, followed by how problems identified by the evaluation will be addressed. Third, we will identify common measures across Cores as a mechanism to simplify the evaluation process. Finally, we will outline our commitment to evaluation by detailing our participation in the national CTSA evaluation.

## **Overall Evaluation**

The University of Pittsburgh is proposing four overarching transformative goals for the CTSI.

1) **Transformation of the *Institution***- The University of Pittsburgh will develop the Clinical and Translational Sciences Institute (CTSI) as the integrative "*academic home*" for the discipline of clinical and translational science in western Pennsylvania.

2) **Transformation of the *Scientist*** – The CTSI will transform the University’s approach to the training of scientists to develop a cadre of biomedical and behavioral scientists in the new discipline of clinical and translational science.

3) **Transformation of the *Research*** – The CTSI will transform the conduct of research by 1) *integrating* existing and being *innovative* in developing new crosscutting research methodologies and tools that will be incorporated into the development of clinical and translational research hypotheses, the promotion of translational science collaborations, the development of research educational initiatives, and the performance and regulation of clinical and translational research, and 2) facilitating the performance of highly innovative and pioneering translational research that can be rapidly developed into new disease preemption and prevention strategies, drugs, devices, diagnostics, and therapeutics and efficiently translated to humans and clinical practice.

4) **Transformation of *Health Practice*** – The CTSI will transform regional health practice by building a "population-based laboratory" through collaborative community-based participatory programs to generate research hypotheses and develop and test new collaborative methods for translation of basic and preclinical scientific discoveries to health practice in western Pennsylvania.

## **1. Transformation of the *Institution***

The first transforming goal is not just achieved by whether the CTSI has designated space; rather, several components need to be evaluated to achieve this goal. The presence of the CTSI as an academic home will be evaluated based on the process, short and long term outcomes. Process measures are those that are necessary to achieve the outcomes. These measures include Institute structure and operations such as conferring secondary academic appointments, participating in promotion and tenure, developing a space plan and strategic plan, recruiting members, planning for additional resources, and establishing a protocol for implementing National CTSA Consortium Best Practices. The evaluation of these indicators will involve a content analysis of the administrative data that will be documented. A short term outcome is having an operational CTSI, which will be measured by counting the number of members, members who have used services, participants in "Synergies in Health Research Day", and multidisciplinary teams that were formed. We will also track the number of grants, papers, and presentations submitted with the help of the CTSI. A long term outcome is moving into the renovated space for the CTSI which will be measured in terms of square footage and the number of researchers from different disciplines who use the space. Other long term outcomes include the CTSI making primary appointments for faculty (evidenced by documentations such as offer letters), establishing a discipline of Clinical and Translational Science (degree granting PhD program), and improving health through research being conducted at the CTSI (as evidenced by publications of CTSI investigators, grants, and clinical practice observed at UPMC).

The governance of the CTSI is also a part of this first goal. In order to evaluate the effectiveness of the governance, we will conduct regular surveys of key stakeholders (Deans, Vice Deans, Directors, Advisory

Boards, Steering Committee, and Executive Committee). The surveys will be anonymous so that participants will be more comfortable in responding accurately. Questions such as their impression of the leadership of the CTSI, the effectiveness of the CTSI at helping trainees, Scholars, and junior faculty establish careers, and the performance of the leadership will be included in the surveys. We will also include several open ended questions so that participants can indicate potential areas to be improved as well as suggestions for improvement. Not only will the overall leadership be evaluated, but similar surveys will be developed for each CTSI Core so that we can evaluate the leadership of each Core. This will provide us with useful information on any potential changes in leadership that need to be considered. The results of the evaluation will be presented to the Steering Committee who in turn will present them to the Senior Vice Chancellor for the Health Sciences.

Finally, in order to facilitate the use of the CTSI, the overall governance of the CTSI is establishing a Research Facilitator program. The Center for Clinical and Translational Informatics (CCTI) will create a tracking system that will be integrated through the Online Resource Community and will document which services are being used in the CTSI. We will also be able to track investigators who are using these services. In order to evaluate the overall usefulness of the CTSI, we will survey investigators from the tracking database. We will ask investigators about which services they have used, their level of satisfaction with the services as well as any suggestions for improvement (including needs that were not met by the CTSI Cores, problems with services provide, and integration of services across Cores.) The results of these surveys will be presented to the Director of the Core and the CTSI Co-Directors and Steering Committee.

The extent to which the remaining goals are achieved involve several key Cores of the CTSI. The evaluations for the key Cores are described in detail below.

## **2. Transformation of the *Scientist***

### **2.A. CTSI Research Education, Training, and Career Development**

To be successful, the formal educational component of the CTSI will provide educational and training opportunities to individuals throughout the University community to: first, expose a wide range of individuals to the exciting possibilities associated with developing careers in clinical and translational research; second, to provide intermediate training to all pre-doctoral students in the spectrum of health research from the bench to trials to incorporation into clinical practice, thus improving the understanding of and dialogue between basic, translational, and clinical researchers; and third, to provide in-depth training in the conduct of high quality clinical as well as translational research at graduate and post-graduate levels.

In the evaluation plan for this Core, we outline five main objectives. For each objective, we present how the evaluation will take place, the key measures that will be assessed, and the potential data sources. Our primary method of data collection will be surveys and curriculum vitas for all of the trainees (including students, residents, K awardees, T32, K30) and Scholars (K12). We believe that in order to get the most accurate data about the trainees and Scholars, we should utilize the most valid data source – the trainee or Scholar themselves. The long term outcomes for the Education Core are to create a discipline of Clinical and Translational Science, generate a well-trained cohort of Clinical and Translational scientists, and make an environment that rewards multidisciplinary research. The measurement of the process to achieve the outcomes and the short and long term outcomes are described under the evaluation of the objectives.

#### **2.A.1.) Curriculum Development**

Evaluating Curriculum Development is critical for several aspects of the education programs. For example, new courses will need to be developed for the PhD program and the core curriculum for all PhD students. Given the importance of these courses, it is critical that the course be evaluated in their development and regularly once they are implemented. Also, the current courses in the K30 need to be evaluated.

**Course Evaluation.** Following the existing K30 program (CRTP) model, we will utilize several forms of evaluation to continuously assess the success of its courses. Core courses are evaluated twice each time they are taught: once midway through the course and again at the end. All other courses are evaluated at the end of the course. The format for all course evaluations is generally the same. Evaluations are anonymous and contain a series of questions consistent across courses and a set of questions that specifically address content in that course. The evaluation includes questions relating to the content and pace of the course, applicability of the material, and quality of the instructor. All provide a space for free form textual critique. Instructors are evaluated on the same form across several dimensions of teaching competence. We will continue to use these evaluations to guide alterations in course content, structure or perhaps even

leadership/instruction. The evaluations will be summarized and reviewed by the leadership. Changes believed to be necessary will be implemented by the Director of the existing Institute for Clinical Research Education (ICRE), Wishwa Kapoor, MD, MPH in conjunction with the Advisory Committee and the course Director.

Existing coursework that is taken in one of the graduate schools will be evaluated by using the standard survey instruments developed by that school. The leadership will review the results of the survey instruments, and the Director of the ICRE will work with the relevant departments to modify the courses if changes are believed to be necessary.

In summary, our course evaluations are excellent. We have used the ongoing evaluation of our curriculum from the participants as a valuable resource. We use their feedback to modify and improve the courses every year. An active curriculum committee for the CRTP (containing two voting trainees) meets monthly to discuss and evaluate ongoing curricular concerns and to propose and implement changes if needed.

***Didactic Program Evaluation.*** The evaluation of the entire didactic program in the CTSI is a more complex task, as the needs of different program participants are potentially quite disparate. However, each year all of the trainees and Scholars who are enrolled in the program will receive a questionnaire related to the goals and objectives of the training program to which they belong to assess whether these goals are being met. Similarly, mentors will be asked to complete a questionnaire to assess whether they believe that their expectations are being met and whether the skills acquired are appropriate. Finally, at 1 and 3 years after completing the program, trainees and Scholars will be surveyed to assess whether the skills they developed and the areas of study they chose were appropriate for their current career positions.

#### **2.A.2.) Responsible research conduct training**

The existing K30 and K12 programs offer several courses that address responsible research conduct training. We will evaluate these courses using the same method as previously described. Given the vast number of courses available to trainees and Scholars, we will track trainees and Scholars training through the tracking system. The tracking system contains information on all of the courses that each person takes. We will review the tracking database regularly to evaluate the extent of training in this area for each trainee and Scholar. We will also monitor all trainees and Scholars on the status of their "Research and Practice Fundamentals" (a web-based training program). Should any issues in the evaluation arise, we will inform the Director of the ICRE. He will address the concern with the trainee or Scholar and their mentors.

We will also evaluate the Research Development Core (RDC) of the K12 (that offers training to Scholars in this area) by two methods. First, we will survey the K12 Scholars to assess the extent to which they have utilized and are satisfied with the RDC services. Second, we will solicit feedback from those in the RDC to ascertain the extent to which Scholars are responsive to their training. The K12 Scholars also report to the advisory committee every six months on their research and training. We will use this meeting as an evaluation of the quality of research and training in which the Scholars are engaged. The advisory committee is expected to provide feedback to the Scholars on the work that they are doing. The minutes from this meeting will serve as our evaluation of the Scholars training and will be reviewed by the evaluation group regularly. Should any issues arise, the Director of the K12 program will be informed and he will meet with the Scholar and the mentoring team to address any issues.

#### **2.A.3.) Minority recruitment and retention**

In order to evaluate the recruitment of minorities, we will track the effort that the ICRE puts forth in recruiting minorities and the number of minorities that are recruited. As outlined in the Research, Training, and Career Development Core, several recruitment strategies will be implemented. First, the ICRE will participate in the EXPORT Center and the Research Career Development Institute for Minorities. We will monitor all of the efforts of ICRE by documenting all meetings that occur through minutes and any other activities in which the ICRE is involved. The second method of recruitment is through the development of the Minority Career Development Program. We will track and evaluate the success of this program by documenting all meetings with minutes, count the number of contacts with minorities, and track the progress of those minorities in the program, throughout their career. A tracking database will be established to monitor the minorities in the program. This information will be reviewed annually with the Director of the ICRE so that we can determine the success of the program and if any changes need to be implemented.

We have baseline data on the extent to which we have been able to recruit minorities. In the K12 program, we have 25% underrepresented minority participation in the first year. We anticipate that we will also have

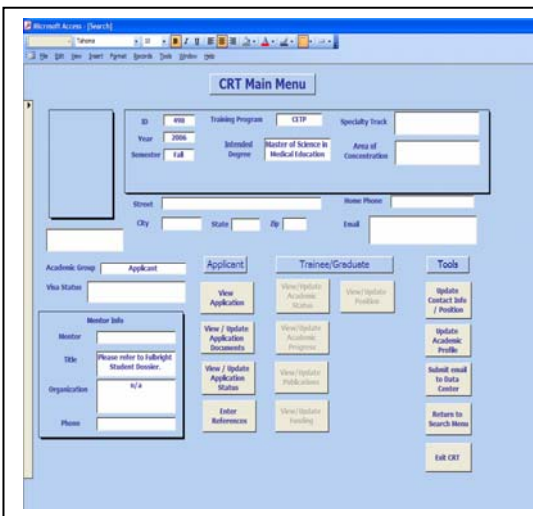
at least that high of a percent in the second cohort. For the K30 program, approximately 50% of trainees have been women and 10% have been underrepresented minorities. In terms of retention, only three minorities have left the program early; that is, they did not complete the requirements for either a master degree or certificate.

In order to evaluate our success at retaining minorities, we will conduct regular focus groups with the minorities in the programs. The facilitator of the focus groups will probe as to what components of the training were most helpful and what might be needed to help minorities. This evaluation effort will focus on generating data that can be used to enhance the programs so that they can be more successful at recruiting and retaining minorities.

#### 2.A.4.) Track T32 trainees and K12 scholars (during training and beyond)

**Tracking system.** We have developed and implemented the infrastructure for a tracking system that contains data collected on enrollment and application (e.g., diversity of backgrounds, demographic data, disciplines, and specialties), on all applicants across all of the programs, as shown in Figure 1. The system was designed so that whenever anyone applies to any of the programs with the electronic application, they are automatically entered into the tracking system. We will design the electronic application for the additional programs proposed to coordinate with this system so that all trainees and Scholars are automatically recorded into the tracking database system once they apply. This enables us to follow applicants and monitor their progress with the application process. Additionally, we can easily document the number of applicants for each of the programs and identify the characteristics of such applicants with a simple report.

**Figure 1**



For those trainees and Scholars who are accepted into the programs, we track their level of training received, progress in their training, any evaluation measures administered, and outcome measures (e.g., academic placement, type of clinical research, publications, grants, and others). The University of Pittsburgh has a registration database with which we can exchange data. This permits us to download information about

the courses and grades received by all of the trainees and Scholars.

We plan on surveying the current trainees and Scholars biannually, as is our current practice in the K12 and soon to be K30. For the K12, we have submitted and obtained approval from the IRB to administer these measures. We are working on an IRB protocol so that we can consent and evaluate the progress of all of our K30 trainees. We will also seek IRB approval to evaluate the T32 trainees. We have measures that are approved by the IRB, which appraise their progress in their training, their level of satisfaction with their training, and the amount of training they have received. These measures will be administered over the web so that they can easily be linked to their tracking information.

The tracking system enables us to follow-up with the trainees and Scholars during and after completing the program. We are able to do regular surveys of current trainees and Scholars and match their survey data with their tracking data. Additionally, we can follow-up trainees and Scholars who have completed the program. With their follow-up data, we can track their career trajectories.

**Tracking of pilot projects.** Many of the trainees and all of the Scholars will be conducting pilot research. We believe that it is important to evaluate the progress and quality of these projects. First, the T32 trainees will be engaged in research with their mentors as well as their dissertation research. While the research will be regularly monitored by the mentors, the trainees will also be required to present their work every six months to the advisory committee. The caliber of their research and the progress will be evaluated through the advisory committee. Minutes will be taken that will be used to track their research.

For the K30 trainees, those seeking a master degree are required to do a thesis. In order to track their research, we require that their proposal must be approved by the committee members before the research begins. The mentoring team monitors the progress of the research. When the project is satisfactorily completed by the trainee, the trainee must defend the thesis to a committee that is comprised of the mentoring team as well as representatives from the K30 group.



For K awardees, including the Scholars, they will present their work every six months to an advisory committee. This process is already in place for the K12 Scholars. The Multidisciplinary Advisory Committee reviews the work accomplished by the Scholar as well as the anticipated work to be completed in the future six months. It is during this time that any committee members can raise concerns or address problems with the Scholar. The mentoring team is also present at the meetings. As with the T32 trainees, minutes are taken and reviewed to evaluate the effectiveness of this forum. In addition, Scholars are asked to review the usefulness of this venue annually. This enables us to evaluate their perceptions on the usefulness of this mechanism. Given the success with which this has been received for the K12 program, the same model will be used for the T32 trainees and other K awardees.

*Career Outcomes of Participants.* We will track the career outcomes of all participants who receive training support through all of the programs proposed. We will maintain a database on the trainees and Scholars and will update it regularly by adding information obtained via direct contact with former trainees and Scholars, survey questionnaires, and the trainees'/ Scholars' curriculum vitae. The information will include positions held, employing institutions, research involvement, percentage of effort in research, grant funding, promotion and tenure, publications, presentations, and other major accomplishments. We are interested in compiling information that will document the career trajectories of the trainees and Scholars. To compare the outcomes of program participants with those of nonparticipants, we will also track similar information from a random sample of postdoctoral trainees, fellows, and junior faculty who were potential candidates but did not receive training in our programs.

#### 2.A.5.) Role of mentors

*Evaluating Progression of the Mentoring Relationship.* The mentoring program will be evaluated in several stages. After initial orientation and training, evaluation will focus on whether the needs of the trainees and Scholars were met, goals were developed for the mentors and mentees, contracts were signed, and support material was adequate. An early progress report will be evaluated at 6-8 weeks to determine whether the mentoring relationship has been initiated, to identify problems and barriers, and to readjust as needed. Early intervention will be provided to mentoring relationships identified to be at risk. In her role as the Director of the CTSI Mentoring Program, Joan Lakoski, PhD will meet with mentors and mentees regularly to ensure that the mentoring goals of the program are being met, ensure that meetings between mentors and mentees are occurring at planned frequencies, and help in conflict resolution and the solution of problems if they arise.

*On-Going Monitoring.* Dr. Lakoski and Dr. Kapoor will meet biannually with each mentee and his or her mentors. In these meetings, mentees and mentors will present their accomplishments to date and assess progress toward achieving milestones. If milestones and accomplishments do not meet expectations, the group will discuss the issues and make plans for improving progress. This method of monitoring progress and the mentoring relationship has proven to be very effective in the BIRCWH K12 program for which Dr. Kapoor serves on the Advisory Board.

*Evaluation of the Mentee and Mentors.* A system to evaluate the mentee and mentors during the course of the relationship and beyond is essential to ensure the ultimate success of the relationship. During the course of the mentor-mentee relationship, the mentee will be evaluated both subjectively and objectively. The subjective measures will consist of 1) a self-evaluation of the mentee's and mentors' success in achieving the goals and fulfilling the responsibilities specified in the learner-centered contract; 2) the mentors' evaluation of the mentee's success in achieving the goals and fulfilling the responsibilities specified in the contract; and 3) the mentee's evaluation of the mentors' success in achieving the goals and fulfilling the responsibilities specified in the contract. The objective measures will consist of 1) academic productivity measured by the number of published research abstracts and presentations at national scientific meetings, the number of peer-reviewed and other manuscripts, the success in obtaining extramural research support, and honors and awards received for clinical multidisciplinary research; and 2) academic appointments and promotions. We will inquire about the frequency and duration of mentor-mentee meetings regarding the development of research projects; the types of assistance given to the mentees, including instructions and discussions concerning responsible conduct of research; and the mentors' impact on the mentee's career development. We also have a measure (Mentorship Effectiveness Scale) that assesses the effectiveness of the mentee-mentor relationship. The results of this evaluation will be regularly reviewed by the ICRE Director and the Director of the mentoring. If any concerns or issues are raised, they will meet with the mentee and mentoring team to devise a plan to resolve such issues.

**Final Mentoring Program Evaluation.** All mentors and mentees will be invited to a final session to provide a conclusion to the mentoring program although we anticipate that informal mentoring relationships may continue. Evaluations will be conducted to assess what worked, what did not work, the gains by the mentee, the skills gained by the mentors, and recommendations for improvement. We will also evaluate the overall program and will recognize the contributions of the participants and mentors through awards and certificates.

The Director of the ICRE and the advisory committee in conjunction with the mentors will work closely with the mentee to review the mentees's past experiences and competencies and career goals and objectives. They will also monitor the mentee's progress as he or she undertakes the training program and, if necessary, modify the didactic training to meet the mentee's needs. The programs will monitor all aspects of the training very closely and intervene when problems are identified or there are conflicts. The Director, working with the advisory committee, will be responsible for making any changes needed in the didactic training program to ensure that career goals are achieved.

#### **2.A.6.) Other Evaluation Efforts**

We will be evaluating several other components of this Core. For the Faculty Development Program, we will track the number of faculty involved and the disciplines they represent. Not only will we measure their satisfaction with the training and the expansion of knowledge gained after training, we will also track their careers in terms of the collaborative research teams, the disciplines represented in those teams, and the extent to which their work is translational. We will measure their satisfaction with training and mentoring as well as their level of knowledge gained immediately following training. Thereafter, we will use biannual surveys for our follow-up methodology.

For other training proposed such as the research coordinator training, undergraduate, and pre-college training, we will measure their level of satisfaction with the training, knowledge gained, and track their careers by administering a survey biannually. The follow-up surveys will enable us to inquire about their career choices, the usefulness of the training they received and the extent to which they are implementing what they learned in their careers.

### **2.B. CTSI Design, Biostatistics, and Clinical Research Ethics (DBE)**

The DBE Core aims to 1) provide centralized services to a cadre of investigators conducting clinical and translational research; 2) develop innovative and creative research programs to develop tools and methods in design, biostatistics, and clinical research ethics and 3) work with the Education Core to provide training and mentoring to trainees, fellows, and junior faculty as well as educate all investigators about the tools and methods developed. The way in which these aims will be achieved is through four main objectives. We outline these objectives and discuss process, short and long term outcomes. Finally, other evaluation efforts for this Core are discussed.

#### **2.B.1.) Support for Clinical Trial Design and Analysis**

We will develop a tracking system that monitors the number of investigators that approach the DBE and the outcome of their interaction. Every initial contact with the DBE will be logged into the tracking system. The investigator will either work with the DBE Core or will be referred to one of the entities. The path taken by the investigator will be tracked so that we can follow-up with the investigator to evaluate the successful provision of services.

When an investigator works with the DBE Core, we will evaluate the extent to which they were satisfied with the services, the level of support provided, and the successful outcome of their work (e.g. publications, grant applications, etc) every six months of the relationship. These same measures will be used when an investigator works with an entity and will be administered annually. We will also evaluate the extent to which the entity has become a part of the investigative team. The productivity and effectiveness of the investigative teams will also be tracked and evaluated via regular surveys of the team members for the long term outcome of building effective multidisciplinary investigative teams.

These measures will enable us to track the effectiveness of the services offered. For the Core, we will regularly review the evaluation of each service provided. If any issues arise, we will address these with the Director of the DBE and the advisory committee. When an entity is involved with an investigator, we will review the evaluation of that entity on a regular basis. If any issues arise, they will be addressed with the Director of the DBE and the leadership of the entity as well as the liaison. Allocation of resources will also

be regularly reviewed. If services are under utilized or over utilized, we will address this with the Steering Committee for the CTSI.

### 2.B.2.) Tools and Methods Supplied

The tools and methods supplied to clinical and translational researchers will vary depending on the amount of research being conducted by the entities. We will evaluate research progress on new tools or methods in clinical and translational research based on several criteria. First, the amount of time that the entities spend on research will be estimated. This will be evaluated by the appointments on calendars, minutes of meetings, and the number of participants at the meetings. Second, we will evaluate the amount of productivity of the collaborative effort. This will be evaluated based on the amount of grant support sought and funded for the project, the number of participants collaborating, and the number of publications obtained. Third, we will evaluate the extent to which this information is disseminated to other researchers. We will survey the investigative team to determine if this work is being presented at the seminars or other workshops, to other investigators or researchers so that it can be implemented in research. Finally, we will evaluate the extent to which the information gleaned from this research is translated to other researchers through publications, presentations, and grant applications, for our long term outcome. We will also use PubMed and other similar databases to determine if these methods have been utilized in others research.

### 2.B.3.) Effectiveness of Research Topics Prioritization

Evaluation of the prioritization of research topics will depend on the category of the investigator (trainee or Scholar, emerging, or senior investigators). The DBE Core will strive to work with all investigators interested in its services whether directly or through links with the entities. However, it will not compromise its research principles or the quality (scientific and ethical) of the proposals or projects to which it contributes. Prioritization of projects, services, and basic needs will be required and evaluated through surveys, meeting notes, interviews, and discussion boards. When seeking DBE services, all investigators will be asked to complete a brief survey on the topic of their proposal including questions about its feasibility, clinical relevance, scientific soundness, creativity and innovation, potential for funding, mentor support, and how it aligns with the CTSI mission.

Prioritization for the research in which trainees and Scholars are involved concerns their ability and resources to conduct their research project, the feasibility of the research, and the level of assistance needed for the study. This stage of training also necessitates the involvement of their mentors. It is imperative that they have strong mentor support for their work. Each trainee, Scholar or junior faculty member will be asked to complete a web-based survey that inquires about the mentor support, resources to conduct the research, their training, and their future goals. This survey also initiates the tracking system for that particular researcher. Prioritization for these investigators revolves around determining what additional education, information or skill they need to complete the proposal as well as on the topic itself. We will evaluate the extent to which the DBE implemented their prioritization schema. This will be done by documenting the process. A tracking system will be created for the DBE that will record each interaction with the trainee, Scholar or junior faculty member. The system will have the prioritization criteria and process outlined so that the person working with the trainee, Scholar, or junior investigator can check off each criteria that is met and can indicate which areas are deficiencies. For example, should a mentor not be involved with the project, the system will indicate the lack of involvement. The tracking system will be regularly reviewed by the DBE Director and the evaluation team.

Emerging investigators who need data management and statistical support for a potential RO1 or similar grant will complete the topic survey on the web, with additional questions focusing on how this project links with their prior work and fits into their long term career objectives. DBE will review the survey and determine 1) whether it passes initial feasibility tests, 2) the specific skills needed to complete the project, and 3) the potential level of effort that will be required. This information will be documented in the tracking system. After meeting with the investigator, DBE will identify the appropriate entity in which to collaborate. The evaluation team will review the topic surveys and the DBE tracking system to evaluate the effectiveness of the prioritization of research topics. Investigators will also be surveyed as to whether they felt the prioritization process was fair, just and equitable. Evaluators will also use these resources to identify gaps in skills needed, and lack of mentors and resources available that adversely impact the prioritization process.

Senior investigators already have a research agenda that has achieved funding support and results are published in peer review journals. Consequently aspects of the prioritization criteria (e.g., clinical relevance) have already been demonstrated.

#### 2.B.4.) Effectiveness of Education in Topics such as Clinical Research Ethics

The DBE Core and entities will educate novice, emerging and senior investigators on topics in biostatistics, research methods, data management, epidemiology and clinical research ethics through seminars and courses and by working directly with DBE staff. Our approach to evaluating formal courses is described in detail under the Research Education, Training, and Career Development Core. Seminars are evaluated by recording attendance and having participants complete evaluation forms. If an individual is unable to attend a seminar in person they can log into a live Webcast, as will be facilitated by the CCTI. Evaluators will have access to information on who logged in, for how long and whether or not they asked questions. Also, all presentations will be archived. Evaluators will know how many times a presentation was accessed and viewers will be asked to complete an evaluation survey before terminating the presentation.

Education on clinical research ethics can involve taking courses through the K30, Clinical Research Training Program or the Center for Bioethics and Health Law (CBHL). Additionally, investigators could utilize one-on-one sessions with the DBE Ethicist, the CBHL Ethics Consultation Service offered by select UPMC hospitals, or online resources such as the NIH "Academic Bioethics Research and Education Resources" site, the American Medical Association's "Virtual Mentor" site and Bioethics.net. Consequently, each investigator may take his/her own path to resolving the research ethics concerns associated with her project. The DBE Ethicist will track the resources used by each investigator and the outcome of the investigator's work. A brief survey will be devised for those who utilize this service to determine the extent to which the service was helpful and to understand what problems and issues investigators are having. Also, tangential data on what ethical issues arose during investigator projects will be documented, such as, DSMB reports with warnings or problems, unique IRB concerns, and needed application of stopping rules.

#### **2.C. CTSI Pilot and Collaborative Translational and Clinical Studies**

The primary aim of the Pilot and Collaborative Core is to develop opportunities for pilot funding that 1) allows exploration of new technologies; 2) allows for exploration of creative multi or interdisciplinary efforts; 3) engages community health professionals in clinical research; and 4) allows team building and utilization of existing translational and clinical resources and services. In order to evaluate these aims, we propose the following objectives:

##### 2.C.1.) Utilization and Satisfaction

In order to measure the utilization and satisfaction with this Core, we will first need to measure the process that occurred. Namely, we will need to measure the level of advertisement that took place, such as workshops held (number attended and their level of satisfaction with workshops) and solicitations issued. For utilization, we will count the number of applications received and number of awards made. In order to determine the effectiveness of the award at facilitating the development of their research programs, we will survey all past awardees and ask them to what extent the pilot funding contributed to the receipt of grants and publications. We will also inquire about their level of satisfaction with this Core. All of the evaluation information will be provided to the Director of the Core and the Steering Committee of the CTSI.

All applicants for the pilot awards will be entered into the tracking system for the CTSI. Therefore, we will be able to document what other services the applicants have used, their level of training, and their academic position. This will enable us to track them over time, for our long term outcome of career success.

##### 2.C.2.) Outcomes

The short term goal for this Core is to fund trainees, Scholars, and junior investigators so that they can engage in pilot research to help further their career goals. This pilot research program is intended to provide sufficient data so that they can apply for external funding. Therefore, we will measure the number of external grant applications that were made following an award. We will also track the number of publications, presentations, and other contributions to research such as awards for this work. In terms of long term outcomes, we anticipate that this pilot funding will eventually lead to greater collaboration between basic and clinical researchers, as well as engagement of community practitioners in the CTSI. We will measure the long term outcomes by not merely the number of publications and grants, but we will also consider the collaborators of this work to determine if they are from different disciplines or the community.

## **2.D. CTSI Regulatory Knowledge and Support**

In the Regulatory Knowledge and Support Core (RKSC), three aims define this Core: 1) provide research regulatory related resources, services, education and training; 2) establish the Regulatory Compliance Facilitator Program; and 3) transform the GCRC Research Subject Advocates into Research Participant Advocates. The achievement of these aims will be evaluated through the demand for services, the functions that the RKSC provides and the extent to which the Core is effective.

### 2.D.1.) Demand

The demand for services of the RKSC will be evaluated by tracking the number of people from the research community, health professionals, and members from the lay community who approach the RKSC. A tracking system will be created for both the Regulatory Compliance Facilitators and Research Participant Advocates so that they can document every contact they have with one of the three stakeholders. The tracking program will enable them to not only record every contact, but also the purpose of the contact and the outcome. This will enable us to determine the extent and purpose of the service. By tracking the services, we will be able to ascertain the demand for such services. In order to determine if the services are being utilized according to the resources appropriated, we will regularly review these data with the Director of the RKSC and the CTSI Directors and Steering Committee.

### 2.D.2.) Function

The RKSC proposes several services for their stakeholders, such as the Investigational New Drug and Investigational Device Exemptions application service, Institutional Data and Safety Monitoring Board, education and training. Through the tracking system, we will be able to determine which services are the most widely used in this Core. We will also be able to determine which services are not utilized. With this information, we can inform the RKSC so that services and functions can be modified accordingly.

### 2.D.3.) Effectiveness

We will also survey those people who have utilized the Core. In the survey, we will ask them which services they used and to what extent were the services useful. We will also inquire as to the extent that the services provided satisfied their need. For example, we would be interested in knowing if they were able to sufficiently navigate through the Institutional Review Board review process as a result of working with the RKSC. We would also ask to what extent they felt their knowledge in the particular area increased as a result of working with the RKSC. Finally, we would ask them to what extent this benefited participants. A significant contribution of this Core would be if the research was revised so that it was safer for participants and ensured their privacy.

The data from the demand and function evaluation are readily available to the RKSC by a report mechanism that is built into the tracking system. Data from the effectiveness evaluation will be regularly reviewed by the Director of the RKSC and the CTSI Steering Committee. The report can be run on a regular basis and changes in services can be implemented when appropriate. Should any issues arise changes in service provision will be explored with the Core Director and the Steering Committee.

## **3. Transformation of Research**

### **3.A. CTSI Novel Clinical and Translational Methodologies**

The Novel Clinical and Translational Methodologies Core aims to: 1) foster the development and dissemination of novel approaches to clinical and translational research, including those that take advantage of the rich infrastructure provided by the participant, clinical, and translational Cores at the University of Pittsburgh and UPMC; and 2) provide a mechanism by which the use of new approaches, technologies, and methods is promoted within the institution. The achievement of these aims will lead to the following long term outcomes: increased incorporation of cutting-edge tools and methodologies in research activities; increase in knowledge about novel methodologies for clinical and translational research on the part of CTSI members; and utilization of these methodologies by other CTASs. We will evaluate these long term outcomes along with short term outcomes and process measures for the formative evaluation. This Core will be evaluated using the following objectives.

#### 3.A.1.) Performance

In the first two years of the Core, two projects are proposed, the CTSI Institutional Research Registry and the CSTI/CMU/Intel Diamond Collaborative Innovation Center. The performance of the registry will be assessed by process measures that will occur in the first two years: developing the registry, advertising and

recruiting of participants (number approached and consented), mailing information to participants, and level of participation by the registrants (e.g., number of contacts from potential participants and registry staff). The short term outcome of the registry is operationalized as the number of investigators using the registry to recruit participants for their research and the number of different research projects using the registry. We will also measure the number of outpatient clinical sites that are administering the registry to patients. Given that it will take the registry two years to be fully actualized, we will measure the short term outcomes beginning in year 3.

The Diamond Collaborative Innovation Center will be evaluated based on the short term outcome of its success in demonstrating the applicability of Interactive Search-Assisted Diagnosis (ISAD) for evaluating breast lesions depicted on mammograms and pathology images. Long term outcomes will be the extension of Diamond-based diagnostic methodologies to a broader range of clinical domains.

Given that this Core is specifically concentrating on Novel methodologies, mere counting the number of applications and number of funded proposals is not appropriate. We will evaluate the proposals that are submitted to determine if they are in fact novel. This will be accomplished by the reviews that are conducted. All proposals will be evaluated in terms of the scope of the work, the interdisciplinary utility, and whether the work is novel and has broad applicability. Long term outcomes will include whether the technologies have been incorporated into future CTSI research and has led to future grants.

### 3.A.2.) Utilization of Outputs

For the long term outcome, we will study the impact of any funded work by the extent to which others have adopted this methodology in their practice or research, as previously discussed. We will also track each funded investigator's work through PubMed and CRISP, to determine the extent to which the investigator continues to pursue work with the particular methodology. These data sources will enable us to also determine if others have adopted this methodology in their work.

### **3.B. CTSI Center for Clinical and Translational Informatics (CCTI)**

As described in the Center for Clinical and Translational Informatics (CCTI), several tools are being created for investigators. The aims of this Core are to: 1) Implement and Maintain Advanced Software Tools and Methodologies; 2) Create an Interoperable Grid Computing Environment for CTSI; 3) Facilitate the Development of and Support for CTSI informatics tools through an Online Research Community. Each of these aims can be evaluated through the following three objectives. Additionally, we will identify other components of this Core that will be evaluated.

#### 3.B.1.) Informatics Performance

This Core proposes to create software, link open source tools utilizing grid computing architecture, and develop an Online Research Community (ORC). The evaluation process for this Core will determine the extent to which this Core is meeting their aims. Usage of these informatics tools can be tracked via the following metrics: attendance at (or viewing of) educational sessions related to the software applications, number of registered users (by department), number of logins per month, number of trials (by research area) in the CTMA database, number of trial participants in the CTMA database, number and types of requests for biospecimens, and G-Forge view/download statistics. In addition, request for administrative support, investigator assistance and education from the ITC will be tracked.

For the linking of open source tools, the applications on the CCTI grid will contain features that permit tracking of usage across domains/resources/users. Usage metrics will be tallied, publicly available, and reviewed at regular intervals by the CCTI.

Both coverage and access metrics will permit us to evaluate the utilization of the ORC. That is, will we seek to determine how comprehensive our databases are by comparing them to other known sources of information (e.g., Office of Faculty Records). In addition we will track online views and searches of the various components. For example, how many visitors view information on the ORC website? After receiving an Intelligent Information Routing recommendation, how many individual clicked through to read more information about the notification?

The proposed metrics and evaluation process will highlight areas where barriers to adoption may exist. For example, if some departments are not entering trials into CTMA at the expected rate, we can interview and observe users from that department. These data may suggest changes that need to be implemented in the software or business process changes that could facilitate adoption. The evaluation will inform us as to

what extent resources are being utilized. The CCTI will hold monthly review meetings to discuss current adoption patterns, to review evaluation findings, and to document and prioritize proposed changes.

### 3.B.2.) Effective Practices of Intra- and Inter-Organizational Sharing of Data

The traditional model of a singular scientist independently collecting and analyzing data is about to undergo an evolutionary change. However, few models exist for intra- and inter-organizational sharing of data. In order to identify effective practices, we will seek to identify teams that are succeeding in this new approach to research. This identification may be facilitated by analysis of utilization patterns or a nomination process. When examples of intra- and inter-organizational sharing of data are identified, we will use interviews with the key players to develop a narrative description of their approach. This narrative will include the investigators' research question, the methods they utilized to identify appropriate data sources and informatics tools, the barriers that they encountered (if any), lessons learned, and research findings. These narratives will be collected and made available to the local and national CTSI communities. By developing and archiving these narratives, it is hoped that others will be able to learn from these pioneers about these new research opportunities and resources. It is also possible that these narratives may be adapted into cases for use in training (e.g., utilizing the narratives to develop a problem-based or case-based learning approach for trainees).

### 3.B.3.) Coordinate with NIH CTSA Informatics Steering Committee

We are committed to working with the NIH CTSA Informatics Steering Committee. The commitment will be evaluated to the extent that the CCTI has

1. Placed all tools in G-Forge for implementation at other CTSA sites
2. Utilized the University of Pittsburgh's CTSI Grid services as an evaluation test bed to propose a CTSA pilot of this infrastructure at an additional location (or two/three) determined by the NIH CSTA Informatics Steering Committee.
3. Supported the educational and training needs of both local and national adopters.

We will also evaluate the participation of the CCTI with the NIH CTSA Steering Committee by documenting the number of contacts with the committee, the number of participants from the CCTI at the annual meetings, and the amount of information exchanged by both email and software shared and utilized by different CTSA sites throughout the country.

### 3.B.4.) Other Evaluation Efforts

In order to determine to what extent we are meeting the needs of the end-users, we will gather qualitative usability data prior to the deployment of these tools. We will use qualitative methods to understand clinical trials workflow across the different university entities. Interview data may illuminate differences in the adoption of these tools after their release. We will also utilize interviews with researchers to assess their initial grid awareness and the envisioned utility of grid computing. A post-implementation set of interviews will assess the actual reported utility of grid computing and the barriers to optimal utilization. For the ORC, we will involve methods such as structured group feedback on ORC plans and designs, interviews, focus groups, and usability testing. Summative evaluation of the ORC will also employ focus groups and interviews (in addition to the informatics performance measures mentioned above)

## **3.C. CTSI Participant and Clinical Interactions Resources (PCIR)**

The evaluation of the Participant and Clinical Interactions Resources Core (PCIR) will be derived from our four aims: 1) provide a range of participant and clinical interaction resources; 2) coordinate participant and clinical interaction resources; 3) collaborate with the Clinical and Translational Informatics Core; and 4) support the research activities of trainees and junior faculty. We will evaluate the extent to which we fulfilled these aims through the following four objectives for evaluation. Finally, we will conclude with other evaluation efforts for this Core.

### 3.C.1.) Availability and Use of Resources

Software tools that currently exist for research and clinical administration in the PCIR Core can readily be adapted for tracking availability and use of resources, and for quantitative evaluation. One current tool is the NCRRC legacy tool, called Center Administrative Management Program (CAMP). CAMP is a program written to manage daily census and protocol information at existing GCRCs. It provides capabilities for entering, viewing, tabulating, and reporting data associated with research visits and cost accounting. A second tool is the Protocol Data Management System (PDMS) developed by the Information Technology

and Biostatistics Core of the existing Adult GCRC. This system is linked to the CTMA-Enterprise Scheduling System, (CTMA-SS) a web-based Cold Fusion application designed to manage patient and resource scheduling for clinical research. PDMS collects protocol data to support nursing and administrative functions in the GCRC. The system also links to the CAMP web-based reporting module. PDMS data is sent to two separate applications: the GCRC Scheduling System and the Research Subject Advocate Data & Safety Monitoring Database. PDMS itself consists of three primary modules, Administration, Nursing Administration, and Nursing. The Administration module defines data about investigators and protocols, including numbers of research protocols, study type (i.e., inpatient, outpatient, offsite research visit), number of research visits, location, key IRB approval dates, and protocol status. Thus, data from the Administration module of PDMS will be particularly useful for tracking and quantitative evaluation of the new PCIR Core.

CAMP and PDMS data are entered daily by administrative and clerical staff at each of the Clinical and Translational Research Centers (CTRCs) within the PCIR Core. Monthly reports will be generated for review by the CTRC Program Directors, the PCIR Core Director, and the PCIR Core Administrator. Summaries of CAMP and PDMS data from all CTRCs will be reviewed at quarterly meetings of the PCIR Core Administrative Coordination Committee, and yearly summaries will be presented to the CTSI Executive Committee by the PCIR Core Director. CTSI Executive Committee feedback on progress and utilization of resources will be funneled back to the individual CTRC Program Directors.

### 3.C.2.) Needs of Research Community and Integration with Other Resources

In order to evaluate the needs of the community, we will conduct surveys of the CTSI investigators. We have a database of all CTSI investigators who have utilized services. This database will enable us to survey these investigators to inquire as to their use of the PCIR Core. For those investigators who have not used the PCIR Core, we will inquire as to why they did not utilize these services. We will ask them if there are services that the PCIR could provide that would be useful in their research.

### 3.C.3.) Standards for Quality of Science

The PCIR has an established mechanism for evaluating the scientific merit of protocols. Each protocol is reviewed by several members of the Scientific Review Committee. Every review provides a written review with a priority score. The proposals are then discussed with the Committee for approval, deferral, or disapproval. The evaluation of this process will be documented by the written reviews and priority scores assigned. We will also conduct a content analysis of the meeting minutes when protocols are discussed in the Committee so that we can document the quality of science that is approved. All of this information is reviewed by the PCIR Administrative Coordination Committee.

The PCIR also has an annual review process to ensure the quality of the science for each protocol. Every year, every investigator needs to submit an IRB renewal for each protocol in which the PCIR is used. The protocols are reviewed at the Scientific Review Committees. As previously described, we will content analyze the reviews and the meeting minutes to document the quality of science being supported by the PCIR. As another measure of quality, we will use the tracking database of the CTSI to survey users of the PCIR to determine which services are used, level of satisfaction with services, helpfulness of the PCIR services in conducting the research, whether roadblocks were removed, and if data were of good quality as a result of participating in the PCIR.

### 3.C.4.) Under-Utilization and Poor Performance

Under-utilization and poor performance will be evaluated on two levels. First, we will evaluate each protocol. Each protocol supported by the PCIR Core will be required annually to submit a copy of IRB renewal information in order to review recruitment, use of resources, and productivity in terms of publications. Protocols with recruitment of less than 50% of the anticipated target will be required to submit a letter of explanation to the Scientific Review Committee indicating reasons for low recruitment and plans for remediation. The Committee will have three options: suspend the protocol; allow continued recruitment; or allow recruitment with stipulations for more frequent reporting on progress. The Committee will also offer suggestions on additional CTSI resources to help improve recruitment. Second, we will evaluate the overall utilization and performance of the PCIR Core. Using the database of the CTSI, we will track the number of research visits for the PCIR. We will compare the usage of the PCIR and contrast it with previous utilization of the GCRCs. We anticipate that we will serve more investigators from different disciplines than was previously served at the existing GCRCs. We will work with PCIR so that we can document the level of their capacity. We will calculate the number of FTEs and the hours worked for



each staff and faculty member. This will enable us to determine how many protocols can be administered by the PCIR at any particular moment. In order to document the adequate utilization of the PCIR, we will compare the actual utilization with the potential utilization. Variances will be reported to the PCIR Core Director, PCIR Core Administrative Coordination Committee, and CTSI Executive Committee for strategic planning. In particular, this information can be used to add, reduce, or shift resources to meet actual investigator needs.

### 3.C.5) Other Evaluation Efforts

The PCIR Core first specific aim addresses the establishment of community based settings for Clinical and Translational Research Centers. The Community CTRC has three components (Community Hospital focusing on Minority Health = Braddock, UPMC Community Clinical practices, Community Centers). The short-term outcome is an established PCIR Core in ONE of each of these settings. Success would be measured by conducting at least one protocol in each setting. For long term outcomes, we anticipate having stable research resources at UPMC and in the community. These would include 5 Clinical and Translational Research Centers at UPMC; stable ongoing collaborations with a primary care physician network for conducting clinical research in offices (part of the Community CTRC); availability of CTRCs in UPMC Hospitals; and CTRCs in 3-4 community centers. This long term outcome will be measured by the number or protocols processed at each site.

### **3.D. CTSI Translational Technologies and Resources (TTTC)**

The Translational Technologies and Resources Core (TTTC) aims to 1) establish mechanisms for assessing the translational resource needs of the CTSI research community and, in response, provide broadly needed resources by developing new core facilities that have the tools, educational programs, and expertise to allow integration of new technologies into translational and clinical research and practice; 2) as appropriate, develop a network of interaction between localized cores that are focused on similar services/disciplines to minimize duplication, enhance efficiency, and broaden access; and 3) develop robust mechanisms for informing the CTSI membership about Core services that are available, with a focus on educating the CTSI research facilitators so as to enhance their effectiveness in referring investigators to available research resources. The overall long term outcome of this Core is to achieve an economy of scale for translational cores within the University. Short term outcomes include the creation of new cores to satisfy investigators needs, integration of existing cores and eliminating duplication, and an increase in knowledge about existing cores as a means to facilitate their utilization. This Core will be evaluated using the following objectives:

#### 3.D.1.) Integration of Resources and Utilization

A database will be developed by the CCTI through the Online Research Community that will contain information about the translational cores that exist within the University. The effectiveness of the database and the integration of resources will be evaluated by surveying the Core leaders of the translational cores registered in the database. When they are asked to submit their information annually, we will include a brief survey as to the effectiveness of the integration of and communication between cores, the elimination of duplicative cores, and the utilization of their core by CTSI investigators. The results of the survey will be presented to the Director of the TTTC, who will in turn, share the evaluation report with the CTSI Steering Committee.

#### 3.D.2.) Flexibility in Types of Resources Offered

A significant contribution of the TTTC is the development of new core facilities that satisfy a need as articulated by the research community. This outcome will be evaluated by surveying the CTSI investigators to determine to what extent the TTTC has been successful at meeting their translational technologies needs. All investigators will be surveyed annually from the Online Research Community database. For those investigators involved in translational research, we will ask specific questions about which core facilities they have used, their level of satisfaction with the core services, and if their knowledge of existing core facilities and cores and services they provide have increased. We will also inquire as to whether the available core facilities met their translational technologies need or if they have additional ideas for new core facilities that would satisfy a particular need.

#### **4. Transformation of the Health Practice**

##### **4.A. CTSI Community PARTners Program**

The Community PARTners Program proposes to develop 1.) a “research informed lay community” that actively participates in (a) clinical research studies, (b) translation of research discoveries to individuals and populations, and (c) the development of clinical and translational research agendas; 2.) a “research informed multidisciplinary health professional community” that actively participates in (a) evidence-based practice that fosters the translation of research findings, (b) study participant recruitment and (c) conduct of clinical research; and 3.) “community-informed researchers” who foster the performance of clinical and translational research by (a) educating, (b) communicating with, and (c) partnering with lay and multidisciplinary health professional communities. In order to evaluate the efforts put forth by this Core, we propose the following objectives:

###### **4.A.1.) Engaged Community**

The community is defined as both the lay community and health professionals. Each of these groups will have their own advisory board. We will evaluate the engagement of the community by the number of members recruited for the advisory boards and their level of participation in the board. We plan to conduct a brief qualitative phone interviews with a small sample of community leaders and providers who after initial contact decided to participate and another small sample of individuals who decided not to participate. For both groups, we would begin by asking informants to explain how they came to this decision and what role followed by specific prompts about other factors that may encourage and discourage providers from participating in studies such as: their perceptions of the CTSI plan, their ability or desire to participate, the potential burden of participation, etc. The information gathered from this brief study would provide subsequent projects a better sense of the kinds of barriers that prevent individuals from participating and a rough sense of their salience. Another method proposed to engage the community is through education. We will track the number of participants in seminars, web-casts and video conferencing. We will also count the number of people who utilize the web-based training. Another level of engagement is the number of participants in the research participant registry. Finally, the centralized repository of resources will be monitored to determine the amount of community resources represented in the repository.

###### **4.A.2.) Trained Investigators**

The training of investigators will occur through education and mentoring. Education involves a certificate program and seminar series. We will evaluate the success of these programs by both the participation in and level of satisfaction with the training. We will also follow-up investigators who have utilized this Core to determine to what extent the training was useful in engaging in community research. Mentoring of investigators will take place with the lay community as well as the health professionals. We will survey both the investigators and the mentors from the lay community and health professionals to get the mentee’s and mentor’s perspective on the experience, level of satisfaction, usefulness, and substantial contribution that the experience had on their research.

###### **4.A.3.) Established Research Priorities**

Both advisory boards of the lay community and health professionals will be establishing research priorities. Meeting minutes will be used to evaluate the prioritization established across these boards. We will collate these priorities and compare them with the research being conducted by the investigators involved in this Core to determine the extent that the priorities and similar with the research being conducted.

##### **4.B. CTSI Catalyst Program**

The CTSI Catalyst Program addresses partnering academia with industry. Two aims make up this Core: 1) to promote training of students and faculty in the health sciences to advance understanding of the role of academic health centers and industry in developing novel therapeutics and diagnostics and 2) to catalyze strategic and proactive engagement with select industry partners in the development of a commercial value chain around our most promising inventions.

The first aim will be evaluated by feedback from participants in the form of evaluations; number of funded investigations with student participation, and satisfaction on the part of the industrial partner. Long term outcomes will be evaluated by the number of patents applied for and the number of patents issued. We will monitor participation in the courses and types of material being developed with our students, residents, fellows and faculty. Up to half of the students activities could be conducted at an individual commercial

partners laboratories and this will be monitored for quality of research experience, surveys of students' response to the experience, and satisfaction of the industrial partner.

The second aim will include programs designed to identify potential projects and funding streams with faculty and students. We will assess the number of programs, dollar amounts of funding, number of applications and meeting of milestones and timelines. All participants within the program will be tracked to determine if additional funding is sought or other partnerships with industry formed. In addition, with biotechnology firms, we will assess the number of funded SBIRs and STTRs. All of the data from the evaluation will be reviewed with the Director of the Core and shared with the Steering Committee of the CTSI.

## 5. Common Measures

Many variables are common across the ten Cores. In this section, we present a table of those common variables and the data sources that will be used to measure the variables. The table demonstrates the consistency of measures used across the Cores. By utilizing common measures, we are able to evaluate the contribution of each Core in the most efficient way possible. In order to effectively evaluate all aspects of the CTSI, it is necessary to utilize common measures. This will allow us to pool data across cores and report data in the aggregate for the entire CTSI, thereby facilitating reporting our outcomes to our stakeholders and other CTSA institutions.

We are measuring several outcomes across all Cores, such as effectiveness. If the outcomes are not reaching the expected goals, RAND will conduct a set of targeted interviews with key players to more specifically identify the potential issues and suggest appropriate intervention options.

**Table 1. Common Measures**

Outcomes	Data Sources	Cores										
		CTSI	EDUC	DBE	Pilot	RKSC	PCR	Novel	CCTI	TTRC	PART	CP
<b>Process</b>												
Appoint/Promotion	Lists	X	X		X							
Strategic Plans	Admin Data	X			X		X		X	X		
Protocols	Content Analysis, # protocols developed	X			X		X					
New Course	Course evaluations		X	X								X
Research Registry	Advertising and recruitment data							X			X	
Educ in New Topics	Participant evaluation forms, Webcast logins, Online Presentation Access,		X	X					X	X	X	X
<b>Short Term</b>												
Publications	PubMed, Ovid, Micromedex	X	X	X	X	X			X			
Presentations	CVs	X	X	X	X	X						
Grants	CRISP	X	X	X	X				X			
Pilot Projects	Mentor & mentee surveys, Committee meeting minutes		X		X							X
Service	# of users, # of sites participating, Tracking program, Teams formed Seminar Attendance, Satisfaction Surveys, CAMP (Center Administrative Management Program), ORC Database	X		X	X	X	X	X	X	X	X	
Course updates	Course evaluations, ICRE Advisory Committee reviews		X	X								
Responsible Research	Ongoing monitoring system, Meeting minutes		X	X	X	X			X		X	X
Minority Participation	Surveys, Participation in EXPORT and Minority Institute		X									
Mentor Teams	Progress reports, Frequency of meetings, Focus groups/interviews, Self evaluations Mentorship Effectiveness Scale		X	X	X						X	X
Quality proposals	Surveys, Meeting minutes, Interviews Discussion Boards, Process documentation, Reviews, IRB Content Analysis		X	X	X	X		X	X	X		
Software and Data Usage	Attendance at training sessions, # of logins, Clinical Trials Management Database (CTMA) G-Forge views and downloads			X			X		X	X		
Effectiveness	Surveys, Interviews, Online suggestion box	X	X	X	X	X	X	X	X	X	X	X
<b>Long Term</b>												
PhD Program	Establishment of	X	X									
Space	Square footage	X										
Faculty	Offer letters	X	X	X	X				X			

Outcomes	Data Sources	Cores										
		CTSI	EDUC	DBE	Pilot	RKSC	PCIR	Novel	CCTI	TTRC	PART	CP
appointments												
Publications	PubMed	X	X	X	X				X			
Clinical Innovations	Grand Rounds, Meeting minutes Seminars, Proposal Evaluations	X			X		X	X		X		
Career and Educational Development	Online investigator tracking system, Surveys, CVs	X	X		X				X	X		
Program Evaluations	Goals and objectives survey, Pre/post surveys	X	X	X	X	X	X	X	X	X	X	X
Research teams	Number formed, Grant submissions, Publications, Author lists, New Center staff teams, Follow-up surveys,		X	X	X		X	X	X	X	X	X

EDUC: Research, Education, Training and Career Development  
Pilot: Pilot and Collaborative Translational and Clinical Studies  
PCIR: Participant and Clinical Interactions Resources  
CCTI: Center for Clinical and Translational Informatics  
PART: Health Community Partners

DBE: Design, Biostatistics and Clinical Research Ethics  
RKSC: Regulatory Knowledge and Support  
Novel: Novel Clinical and Translational Methodologies  
TTRC: Translational Technologies and Resources  
CP: CTSI Catalyst Program

## **6. Informed Consent**

Obtaining IRB approval to conduct this evaluation is critical as sensitive information will be collected. Because of this, we will seek informed consent from those who agree to participate. Participants will be asked to sign IRB approved informed consent when they approach the CTSI. We will explain to them that their participation is strictly voluntary and in no way impacts their involvement with the CTSI. We have already obtained IRB approval to conduct our evaluation of the Roadmap K12 program and have obtained consent by the Scholars. We are extending this work to the K30 program and the Building Interdisciplinary Research Careers In Women's Health (BRICWH) K12 program and are in the process of obtaining IRB approval to evaluate those programs.

The Director of the IRB is fully engaged in development of the CTSI and conversations have already been initiated about obtaining IRB approval with informed consent for the participants. All data will be kept confidential and results will only be reported in aggregate. Given that the evaluation is both formative and summative, participants who are involved in the CTSI Research Education, Training and Career Development Core will be informed that their individual data may be shared with the leadership of this Core so that interventions can be developed on an individualized basis if necessary. This Core is focused on the success of all of their participants. As such, certain issues will need to be shared with the leadership (e.g., issues with mentoring, number of publications, etc). All other data will be shared with the Director of each of the Cores and the Steering Committee in aggregate form.

## **7. National CTSA Evaluation**

Evaluation is a critical component to the success of the CTSI at the University of Pittsburgh. We are committed to evaluating the CTSI as the evaluation will inform us as to the elements in the CTSI that are successful and those that can be improved. We will identify our successes and most effective strategies and share those with CTSA nationally to further transform the research enterprise.

The CTSA is a national effort, and as such, numerous institutions will be funded across the country. Given this innovative approach to overcoming barriers for clinical and translational research, we believe that it is critical for a national evaluation to be conducted. A national evaluation will provide information on what models lead to eliminating barriers in clinical and translational research, facilitating multidisciplinary research, and creating a discipline of Clinical and Translational Science. It is only through a national evaluation that appropriate data can be generated to determine the worth of funding this initiative. Congress and other constituents will need to know to what extent the CTSA have been successful across the country.

As evidenced by Dr. Rubio's active participation in the Trans-National Evaluation Workgroup for the Roadmap K12 (as the Chair of the Evaluation Liaison, Dr. Rubio was a member of this group), we will participate fully with the National CTSA evaluation. Moreover, from our experience in the National evaluation, we value the opportunity to work with our colleagues at other institutions so that we can learn from each other about and implement the best methods for evaluation.

## Implementation Plan.

As one of the nation's leading academic research centers, the University of Pittsburgh has both an opportunity and an obligation to take the inherent risks associated with reengineering a successful research enterprise to undertake a transformative initiative that will result in the development and advancement of clinical and translational science as a distinct discipline in western Pennsylvania. The University is committed to transforming its culture, environment, and structure to achieve this goal by forming the Clinical and Translational Science Institute (CTSI). The transformation that will be catalyzed by the CTSI will result in fundamental changes in the *institution* and its training of *scientists*, its performance of *research*, and its *health practice* through an unprecedented collaborative effort among the six schools of the health sciences (Dental Medicine; Health and Rehabilitation Sciences; Medicine; Nursing; Pharmacy; and Public Health); the University of Pittsburgh Medical Center (UPMC), one of the nation's largest and most financially successful academic health care systems; RAND; Carnegie Mellon University (CMU); and local health professionals, foundations, lay communities, and industry. The primary focus of the CTSI is to develop, nurture, and support a cadre of highly trained clinical and translational scientists by building on the University's established record of clinical and translational research training, including its existing K30 and Roadmap K12 Clinical Research Training Programs, and its extensive resources. Through "*integration and innovation*," the CTSI will excel in the development of new biomedical knowledge and the translation of that knowledge from the basic and preclinical research settings to individuals, communities, and health practice. This will be accomplished by transforming the University of Pittsburgh's extensive activities in basic, translational, and clinical biomedical research through novel institutional *integration* of existing programs and the development of *innovative* interdisciplinary research initiatives. The resulting transformation will impact on health locally, regionally, and nationally.

## Goals

The University of Pittsburgh is committed to transforming its culture, environment, and structure to develop clinical and translational science as a distinct discipline through the formation of the CTSI. Specific goals of this transformation are:

**1) Transformation of the *Institution***- The University of Pittsburgh will develop the Clinical and Translational Sciences Institute (CTSI) as the integrative "*academic home*" for the discipline of clinical and translational science in western Pennsylvania.

**2) Transformation of the *Scientist*** – The CTSI will transform the University's approach to the training of scientists to develop a cadre of biomedical and behavioral scientists in the new discipline of clinical and translational science.

**3) Transformation of the *Research*** – The CTSI will transform the conduct of research by 1) *integrating* existing and being *innovative* in developing new crosscutting research methodologies and tools that will be incorporated into the development of clinical and translational research hypotheses, the promotion of translational science collaborations, the development of research educational initiatives, and the performance and regulation of clinical and translational research, and 2) *facilitating* the performance of highly innovative and pioneering translational research that can be rapidly developed into new disease preemption and prevention strategies, drugs, devices, diagnostics, and therapeutics and efficiently translated to humans and clinical practice.

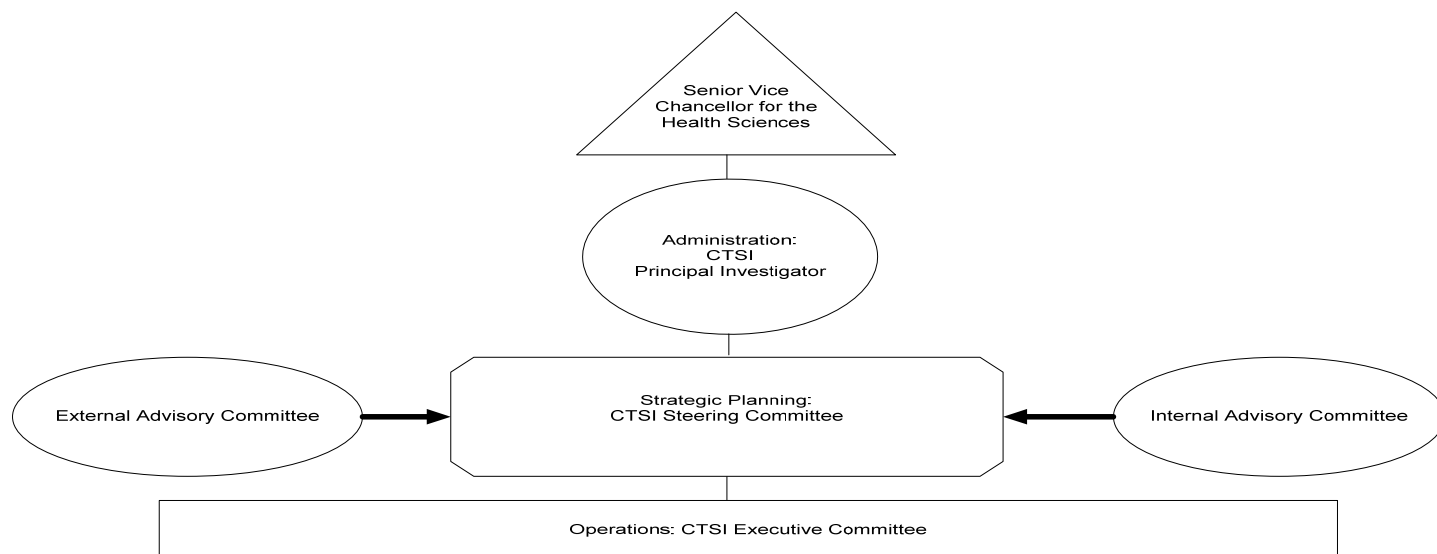
**4) Transformation of Health Practice** – The CTSI will transform regional health practice by building a "population-based laboratory" through collaborative community-based participatory programs to generate research hypotheses and develop and test new collaborative methods for translation of basic and preclinical scientific discoveries to health practice in western Pennsylvania.

## Implementation Process and Integration into the Institution's Strategic Plan.

**Guiding Principles.** The CTSI implementation plan establishes a collaborative performance-based framework for achieving the CTSI's four transformative goals. By design, this dynamic plan will be responsive to the formative CTSI/RAND Evaluation Program; the multidisciplinary Internal Advisory Committee (IAC); the CTSI External Advisory Board; the ever-changing needs of trainees and investigators; advancements in the

biomedical and behavioral sciences; identified barriers to research training and performance; the availability of resources; and priorities of the CTSA National Steering Committee and National Institutes of Health. During the first six months of funding (“Planning Phase”), the CTSI will establish management procedures; design its administrative infrastructure; develop a formal strategic plan; collaborate closely with the University of Pittsburgh schools of health sciences to integrate existing resources in a unified manner; and plan the development of new infrastructure that is required to complement existing resources. During months 7 to 24 (“Implementation Phase”), CTSI plans will be implemented and integrated into the institution’s strategic plans. Formative evaluation of the CTSI and its programs during the Implementation Phase is expected to generate information that will result in timely modification of the plans; initiatives; and programs of the integrative CTSI and its components. It is anticipated that substantive modifications to the institute and its programs will be made during the Implementation Phase. The “Operational Phase” of the CTSI will begin in month 25 and will implement the modified CTSI plans and include mechanisms to adapt to results from the longitudinal evaluation process.

**Implementation Process.** To achieve the four overall goals of the CTSI and the specific aims of its ten key functions (CTSI Cores), the implementation plan must initially focus on the development of the administrative structure; infrastructure; and resources that will establish the CTSI as a distinct interdisciplinary institutional entity external to any individual school, department, division, center, and program at the University of Pittsburgh. The first step in this process will be the establishment of the CTSI administrative and advisory structures (Figure). The *CTSI Steering Committee* will be responsible for 1) strategic planning; 2) addressing operational issues and proposals that are developed by the operational *CTSI Executive Committee*; and 3) developing and implementing substantive plans in response to the results of the formal CTSI /RAND Evaluation Program. These functions will be supported by the Steering Committee’s ability to rebudget program funds and to modify; develop new; or deactivate CTSI cores and components based on objective evaluations of utilization; productivity; quality; and dynamic changes in the needs of investigators and trainees. The Steering Committee will be composed of the CTSI PI (chair), Institute Co-Directors for each of its 4 key elements (Education and Career Development; Translational Research; Clinical Research; Clinical and Translational Informatics); the six deans of the schools of the health sciences; and the Senior Vice President, Quality Care and Chief Medical Officer of the University of Pittsburgh Medical Center (UPMC). The Steering Committee will receive guidance from the multidisciplinary Internal Advisory Committee which is composed of senior and junior translational scientists from each health sciences school, CTSI Scholars, respected community leaders, representatives from corporate Pittsburgh, a RAND designee, and senior UPMC administrators. An External Advisory Board (to be named) will also provide substantive input into the strategic plans of the CTSI. Operationally, strategic plans will be implemented by the CTSI Executive Committee, which is composed of the PI; Co-Directors; and Directors of each CTSI Core.



The PI and Associate Vice Chancellor for Clinical Research, Health Sciences, Steven E. Reis, MD, has transcendent institutional responsibility for the clinical research enterprise across the six schools of the health sciences at the University of Pittsburgh. Accordingly, he will be responsible for acting on behalf of the Steering Committee to implement administrative plans that are necessary to catalyze the integration of the CTSI into

the institution's strategic plan. Early in the Implementation Phase, these administrative activities will result in modifications in and the development of new University policies and procedures that will culminate in the establishment of the CTSI as an independent institutional entity. These activities will provide the CTSI with the ability to play an integral role in institutional processes such as promotions and tenure; establishing institutional research priorities; education and training of clinical and translational scientists; faculty recruitment and retention; and development of research resources and facilities as described elsewhere in this application. For example, changes in University procedure will grant the CTSI the ability to confer secondary academic appointments in "Clinical and Translational Science" which will establish clinical and translational science as a distinct discipline in the University. In addition, each of the six schools of the health sciences will amend its bylaws, as needed, to allow the CTSI Steering Committee to actively participate in its promotions and tenure processes by having the ability to 1) nominate a CTSI member for promotion and tenure in her/his primary department; 2) provide *ad hoc* members to departmental promotions committees; 3) identify references from local and national clinical and translational science communities; and 4) formally submit letters supporting promotions and tenure. These nontrivial, unprecedented changes in policies and procedures at the University will result in a change in institutional culture that nurtures the academic career development of clinical and translational scientists and, in turn, the establishment of clinical and translational science as a distinct discipline.

The CTSI is uniquely suited to catalyze these types of changes in institutional policies and procedures that support the development of clinical and translational science as a distinct and respected discipline. The CTSI PI will report directly to the Senior Vice Chancellor for the Health Sciences (SVCHS), Arthur S. Levine, MD, who has transcendent administrative responsibility for the six schools of the health sciences. The SVCHS's unequivocal support for the CTSI, which is explicitly stated in his letter that is included with this application, provides the CTSI leadership with institutional authority to implement the administrative changes that are proposed in this application. Furthermore, the University administrative structure will provide a foundation for implementation of other major interdisciplinary CTSI initiatives. For example, the proposed CTSI T32 training program will develop and implement a common core clinical and translational science curriculum in the six schools of the health sciences. This effort will be facilitated by the roles that the six deans will play on the CTSI Steering Committee and will be implemented under the auspices of the SVCHS. Similarly, the SVCHS will integrate CTSI leadership into institutional decision-making processes for the development of core clinical and translational research resources; the recruitment of faculty; and establishing interdisciplinary research programs. This institutional administrative structure ensures the successful establishment and long-term viability of the CTSI as an independent institutional entity.

Effective implementation of CTSI plans will have an impact on communities external to the University. As a result of the interdependence between the University of Pittsburgh and its health care partner, the University of Pittsburgh Medical Center (UPMC), CTSI initiatives rely heavily on access to UPMC resources, including patients to participate in research studies; health professionals; facilities (e.g., hospitals; community outpatient offices); funding (e.g., endowment of the CMRF Pilot Studies fund; support for the development of interdisciplinary research programs); and its electronic health record. UPMC's administrative structure ensures access to these resources and the integration of the CTSI into UPMC initiatives and activities. The President of UPMC, Mr. Jeffrey Romoff has committed UPMC to play an integral role in the CTSI as is indicated in his letter of support that is included with this application. In addition, UPMC has charged its Senior Vice President, Quality Care and Chief Medical Officer, Loren Roth, MD, MPH, to serve on the CTSI Steering Committee to ensure seamless integration between CTSI and UPMC initiatives and provide access to and support from UPMC. Dr. Roth's academic role as the Associate Senior Vice Chancellor for the Health Sciences under the direction of the SVCHS demonstrates the seamless integration of UPMC and University administration at the highest level.

Implementation of the CTSI's Strategic Plans will also require close collaborations with the local community and industry. The Co-Director of the CTSI Community PARTners Core is Mr. Lee Hipps, Executive Vice President and Chief Operating Officer of the Urban League of Pittsburgh. The Urban League has played a central role as an advocate and direct service provider in areas basic to human life (health and welfare; employment; education; housing) in Pittsburgh since 1918. In addition to playing an integral role in the logistical implementation of CTSI plans (e.g., serving as a community site for participant recruitment; study performance; and health screenings and education), the Urban League will serve as a link between the CTSI and other community organizations. Similarly, representatives of corporate Pittsburgh and local foundations will serve on the CTSI Internal Advisory Committee to provide guidance and serve as liaisons to the local community. This process began as part of the CTSI planning process which involved a meeting of corporate, foundation, and organization leaders including the President and CEO of NOVA Chemicals; Director of

Sustainable Pittsburgh; President and CEO of Ceeva; and the Director of the Scaife Family Charitable Foundation to discuss plans for integration of the CTSI into the corporate and foundation communities. In addition, the established Office of Enterprise Development, Health Sciences, will serve as the liaison between the CTSI and the biomedical and biotechnology industry.

**Specific Implementation Plans.** As noted above, implementation of the CTSI plans must begin with the development of its administrative structure and its establishment as an independent institutional entity. Specific details for the Planning; Implantation; and Operational Phases are listed below:

<b>Planning Phase (Month 0-6)</b>	<b>Implementation Phase (Month 7-24)</b>	<b>Operational Phase (&gt;Month 24)</b>
Establish Administrative Structure	Implement Space Plan (Phase 1)	Implement long-term strategic plans
Convene Internal Advisory Committee	Recruit CTSI Members; Assoc. Members; Scholars; Affiliates	Member recruitment & retention
Convene External Advisory Committee	Effect changes in University policies and processes (e.g., amend bylaws in schools of the health sciences)	Implement changes in administration, programs, projects & initiatives in response to evaluations
Leadership Retreat	Promote CTSI and its functions	Implement Space Plan (Phase 2)
Develop Strategic Plan	Implement Short-term Strategic Plans, including establishment of 10 Core functions	
Develop Operations /Policy Manual	Establish links with external stakeholders (e.g., Community organizations; health professionals; industry)	
Hire staff	Initiate CTSI/RAND Evaluation Program	
Reconfigure existing programs (e.g., GCRC, K12 , K30)	Establish University recognition of CTSI as independent entity	
Integrate existing resources (e.g., Office of Clinical Research and components of Office of Academic Career Development; Office of Research, Health Sciences)	Implement changes in response to Evaluation Program and best practices and policies from CTSA Steering Committee	
Space Planning (Phase 1)		
Develop faculty recruitment plan		
Prioritize development of new innovative resources		
Secure institutional commitments (e.g., funds, space)		
Develop policies to respond to Evaluation Program; incorporate best practices from CTSA Steering Committee; identity & address investigators' needs		

(Continued on next page)



Each of the ten CTSI Cores will develop and implement specific plans to achieve its aims. Details of specific plans for each CTSI Core are outlined in their respective sections throughout this application. To ensure that the Cores effectively implement their plans in a coordinated manner, the CTSI has developed standardized milestones that will be adopted by each Core and will assist the CTSI Steering Committee in its strategic planning.

<b>Planning Phase (Month 0-6)</b>	<b>Implementation Phase (Month 7-24)</b>	<b>Operational Phase (&gt;Month 24)</b>
Develop and finalize a program description that incorporates: -administrative structure with corresponding responsibilities -a detailed implementation and management plan for each project that will be implemented under the auspices of the core -performance standards, benchmarks, and milestones	Assemble and train the program team	Full implementation of program activities.
Develop standard operating procedures that address general program operations and administration, including responses to changing needs of members and results from CTSI/RAND Evaluation Program	Formalize collaborative partnerships and integrate relevant existing resources	Conduct process and outcome evaluations and use evaluation results to guide program modifications
Obtain Steering Committee approval of program description and standard operating procedures to ensure the goals of the Core are consistent with the overall vision and goals of the of the CTSI	Begin implementation of program/project activities as outlined in the project plan (this can include alpha and beta testing)	Submit annual progress reports and revised strategic plans
	Develop standard operating procedures that address specific project functions	
	Conduct formative and process evaluations and use evaluation results to guide program development and modification	
	Submit a progress report at months 12, 18, and 24.	

**Other Resources Employed During the Implementation Plan.** The CTSI Implementation Plan will require the use of resources external to the CTSI. The CTSI will leverage existing transcendent institutional administrative offices that can facilitate changes in University policy; implement CTSI plans to promote academic career development; guide and implement space plans and resource development; and launch specific CTSI initiatives (e.g., “Synergies in Health Sciences Research Day“; collaborations with industry partners). These resources will complement the institutional commitment to other aspects of the CTSI that is outlined in the Overall Integrated Approach/Governance section of this application. The Senior Vice Chancellor for the Health Sciences has previously established several offices with transcendent responsibilities across the health sciences schools that will provide resources (e.g., expertise; personnel; space; funding) to implement the CTSI proposal. These include:

**1) Office of Clinical Research, Health Sciences (OCR)** –OCR will serve as the administrative home for the CTSI. As part of the cost sharing arrangement and additional institutional commitments to the CTSI that are outlined in the Overall Integrated Approach/Governance section of this application, a substantial proportion of the OCR’s staff, resources, and services will committed to support implementation of the CTSI’s administrative and clinical and translational research programs. OCR’s office space will contribute to the 2,554 sq. ft. of space that will be dedicated to CTSI administration during the Phase 1 Space Plan.

**2) Office of Research, Health Sciences (OORHS)**– OORHS will lead the development of translational core facilities; administer the CTSI Pilot and Collaborative Studies Program and Novel Clinical and Translational Methodologies Core; and plan and build CTSI’s physical “home” as outlined in the CTSI space plan. These efforts will be supported by the dedication of OORHS staff and resources in a cost sharing arrangement. OORHS will also provide additional expertise (OORHS Manager for Space and Research Resources; OORHS Project Coordinator and Space Planner) during implementation of the CTSI space plan.

**3) Office of Academic Career Development, Health Sciences (OACD)** - OACD will serve as the CTSI's hub for comprehensive academic career development in the discipline of clinical and translational science. OACD's \$\_\_ annual budget and 703 sq.ft. currently serve to support the career development of basic, translational, and clinical scientists. Appropriate effort will be dedicated to implement the career development plans for CTSI Scholars, members, and health sciences faculty who conduct clinical and translational research.

**4) Center for Continuing Education in the Health Sciences (CCEHS)** - In the CTSI, CCEHS will serve as a core resource to implement CTSI plans to promote interdisciplinary and evidence-based practice education; translate research findings to practicing health professionals; and to organize the annual CTSI "Synergies in Health Sciences Research Day" Staff will be dedicated to support these activities as needed.

**5) Office of Enterprise Development, Health Sciences (OED)** - OED programs catalyze academic-industry collaborations and will serve as a framework for the CTSI Catalyst Program. Portions of effort of the five OED staff members will be dedicated to build relationships with industry partners that will be used to implement CTSI programs.

**6) Office of Academic Affairs, Health Sciences (OAA)**- In addition to its role in organizing CTSI seminar programs and planning CTSI Synergies in Health Research Day, OAA will facilitate interactions with University administration. OAA is a key link between the health sciences administration and University administration and will serve as a liaison for the CTSI for the implementation of plans to integrate the CTSI into the University structure. Appropriate effort will be dedicated to this role.

- **Milestones and Alternative Plans if Goals Not Achieved**

The tables on the subsequent pages outline milestones for the implementation of the overall CTSI and its individual Cores. Given the size and complexity of the CTSI and the extent to which it will transform the institution, scientist, research, and health practice, it is likely that several milestones may not be achieved within the proposed timeframes. Alternative plans if goals are not achieved are provided for several milestones. **However, more specific alternative plans to achieve milestones will be developed prospectively in response to results from comprehensive longitudinal systematic evaluations of the CTSI and its components.** The CTSI Evaluation Program, in partnership with RAND, will develop and implement a longitudinal formative and summative evaluation program that will provide outcomes data such as quality, productivity, and achievement of objectives of the CTSI, CTSI leadership, core programs and resources, members, and stakeholders. The CTSI Evaluation Core's approach, which uses a Logic Model evaluation process, is based on the experience of its Director as the chair of the Evaluation Liaisons Committee across the 12 Institutions funded for the Roadmap K12. While other models exist for evaluation (e.g., logical framework, cluster evaluation, and case study), *the logic model offers the best approach for tracking measures within programs over time and monitoring changes in performance for different comparison groups.* The logic model offers flexibility to adapt the evaluation strategy as the activities and/or outcomes change. In creating a transformative CTSI, it is anticipated that adjustments will need to be made. The logic model will reflect those changes and yield useful data without compromising the overall evaluation strategy. The primary goal of the evaluation program is to identify ways to improve the CTSI (Formative evaluation). The secondary aim is to measure the impact of the CTSI on clinical and translational research (Summative evaluation). These aims will assess the administrative and scientific functioning of the CTSI as well as its accomplishments. Results from the systematic evaluation process will guide the development of specific alternative plans if the CTSI goals are not achieved or its milestones are not met.

The CTSI Administrative and Governance Structures have mechanisms in place that will assess outcomes data that are developed by the Evaluation Program. These data will serve to inform the CTSI PI, Steering Committee and Advisory Committees about ways that the CTSI can be enhanced to achieve its milestones, improve its mission, and redistribute resources. This dynamic process is made possible by the scope of resources that is available to the CTSI, the institutional commitment to the CTSI, and the transcendent institutional responsibility of the CTSI PI for the clinical research enterprise at the University of Pittsburgh.

### Milestones for the overall CTSI.

Year 01	Year 02	Year 03	Year 04	Year 05-
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				<b>10</b>
Establish Administrative Structure	Initiate Implementation of Space Plan <i>Alt: Operate in existing space &amp; implement plan in year 3.</i>	Increased membership	≥5 members promoted <i>Alt: Reevaluate membership criteria and CTSI integration into promotions/ tenure process</i>	See note*
Convene advisory committees	Begin CTSI member recruitment and confer appointments in Clinical and Translational Science <i>Alt: Defer until year 3</i>	Document usage of CTSI Cores and Programs	Increased usage of CTSI Cores and Programs <i>Alt: Reevaluate functions &amp; need, and funding for underused Cores</i>	
Participate on National CTSA Steering Committee	Effect changes in University policy related to promotions/tenure processes <i>Alt: Investigate feasibility of development of CTSI as primary department (note: will limit interdisciplinary nature of institute)</i>	Participate in promotions/tenure processes for members <i>Alt: Submit letters in support of members promotions</i>	Implement Space Plan Phase2 <i>Alt: Continue operating using Phase 1 Space Plan until renovations completed or more suitable space identified</i>	
Develop Strategic Plan and Operations/Policy Manual	Implement CTSI cores and programs <i>Alt: Reassess priorities and revise plans for Core resources</i>	Increase # appointments in Clinical and Translational Science	Achieve short-term strategic plan goals <i>Alt: Reevaluate Strategic Plan</i>	
Reconfigure Existing Programs (GCRC; K12; K30)	Hold first Synergies in Health Research Day <i>Alt: Establish CTSI sessions at annual University "Science Day" program</i>	Implement best practices identified by CTSA Steering Committee	Implement changes in administration, programs, projects, and initiatives in response to evaluations	
Develop: Space Plan Faculty Recruitment Plan	Establish University recognition of CTSI <i>Alt: Defer until year 3</i>	Modify plans in response to evaluation process	Increase usage of Research Facilitator Program <i>Alt: Reeval. needs, effectiveness &amp; promotion; deactivate service</i>	
Secure institutional commitment	Initiate annual evaluations of CTSI PI, Co-Directors, Core Directors	Increase usage of Research Facilitator Program <i>Alt: Reeval. needs &amp; pgm promotion</i>	Implement new best practices identified by CTSA Steering Committee	
Establish links with external stakeholders	Initiate annual evaluations of CTSI Cores	Implement new policies of CTSA Steering Committee	Implement new policies of CTSA Steering Committee	
Implement RAND/CTSI Evaluation Program	Establish Research Facilitator Program			
Implement policies of CTSA Steering Committee	Implement new policies of CTSA Steering Committee			

\*Note: Years 5-10- Intermediate and long-term outcomes that are outlined in the CTSI Strategic Plan that is to be developed during the Planning Phase will be achieved. Alt = Alternative plan if milestone not achieved.

**Milestones for CTSI Cores.**

<b>Core</b>	<b>Year 01</b>	<b>Year 02</b>	<b>Year 03</b>	<b>Year 04</b>	<b>Year 05-10</b>
<b>CTSI Research Education, Training &amp; Career Development</b>	-Administrative & operational framework established -Curricula developed -Academic career development plan developed	-Exposure program deployed -Core curriculum implemented in schools of health sciences <i>Alt: Reevaluate needs of predoc trainees in each school</i> - Academic career development plan implemented	-Parallel implementation of educational programs for all educational levels <i>Alt: Reevaluate needs and assess barriers to implementation; modify goals and programs as needed</i>	- Deployment of all educational programs <i>Alt: Reevaluate needs and assess barriers to implementation; modify goals and programs as needed</i>	-See note*
<b>CTSI Design, Biostatistics, &amp; Research Ethics</b>	-Administrative & operational framework established	-Seminar series launched -Initial pilot proposal submitted to CMRF -Implementation of plans to provide services	-At least one DBE research project formulated - CTSI Scholars serviced <i>Alt: Redeploy resources into alt. HS pgms.</i>	-Documented increase in service use <i>Alt: Redeploy resources into alternative support programs in health sciences schools</i>	-See note*
<b>Pilot &amp; Collaborative Translational &amp; Clinical Studies We need to discuss this; problems</b>	- Administrative and Operational framework established - RFAs issued - First round of projects funded - CTSI-log development initiated	- CTSI-log deployed <i>Alternative: Reassess virtual methods to increase collaborations</i> - CITB initiated - RFA(s) issued - Projects funded	- Evaluate success of CTSI-log for increasing collaborations; explore additional mechanisms if so indicated -RFA(s) issued - Projects funded <i>Alt: Reassess funding categories &amp; methods to promote programs</i> -CITB active	-RFAs issued - Projects funded <i>Alt: Reassess funding categories &amp; methods to promote programs</i> -CITB active	-See note*
<b>Regulatory Knowledge &amp; Support</b>	-Administrative & operational framework established	-Planned services deployed	-Documented increase in service use <i>Alt: Reassess programs &amp; needs of investigators &amp; staff</i>	-Documented increase in service use <i>Alt: Reassess programs &amp; needs of investigators &amp; staff</i>	-See note*
<b>CTSI Center for Clinical &amp; Translational Informatics</b>	-Operational framework and infrastructure established	-CTMA deployed - CTSI Online Research Community deployed - Identify needs for	-ORC operational <i>Alt: Develop alt. software</i> -Stage I CME development	-Educational components of ORC deployed Increased use of CTMA & other programs	-See note*

		new informatics tools	complete -Begin new tool development	<i>Alt: Reeval needs, pgms., support</i>	
<b>Participant &amp; Clinical Interactions Resources</b>	-Administrative & operational framework of existing GCRCs restructured	-Braddock Community-Hospital CTRC Operational <i>Alt: Reeval needs &amp; reallocate funds</i> -Short term outcomes met	-1 Community-center based pgm operational <i>Alt: Reeval needs &amp; reallocate funds</i> -Data management system operational -Increased use of CTRCs <i>Alt: Reeval needs &amp; reallocate funds</i>	-1 Community-practice based CRTC operational <i>Alt: Reeval needs &amp; reallocate funds</i> -Documented increase in service use <i>Alt: Reeval needs &amp; reallocate funds</i>	-See note*
<b>Novel Clinical &amp; Translational Methodologies</b>	- Administrative & Operational framework established - 2 Novel Methodologies projects initiated (Registry and Diamond)	- RFA issued and concepts evaluated for year 03 funding - Registry completed <i>Alt: Steps in registry development re-evaluated and project period extended</i>	- Diamond project completed - 1 new program funded - RFA issued and concepts evaluated for year 04 funding <i>Alt: Reassess methods to develop ideas for new methodologies</i>	- Project sponsored in year 03 completed <i>Alt: steps in development re-evaluated and project period extended</i> - RFA issued and concepts evaluated for year 05 funding	-See note*
<b>Translational Technologies and Resources</b>	-Administrative & operational framework established - Concepts for new core facilities solicited and evaluated - Business plan for new facility development - First new core facility initiated - Baseline data of cores developed	- First new core facility prepares for transition to non-CTSI funding mechanism <i>Alt: Additional CTSI funding requested and approved</i> - Consolidation of cores initiated - Updates of baseline data requested/obtained - Educational activities planned	- Concepts for new core facilities solicited and evaluated - Business plan for new facility development - New core facility initiated - Educational programs initiated	- Second new core facility prepares for transition to non-CTSI funding mechanism <i>Alt: Additional CTSI funding requested and approved</i>	-See note*
<b>Community PARTners Program</b>	-Administrative & operational framework established -Advisory boards established	-Pilot community-based home operational -COSB launched -Pilot EBP project launched	-Documented increase in service use <i>Alt: Reeval. needs &amp; pgm promotion</i>	-Documented increase in service use -Additional community-based sites identified <i>Alt: Reallocate</i>	-See note*

				<i>funds</i>	
<b>CTSI Catalyst Program</b>	-Administrative & operational framework established -Establish industry relationships via OED & OTM - Develop training curriculum	-Initial round of student training grants awarded <i>Alt: Modify curriculum</i> -Initial pilot research project funded	-Documented increase in research project solicitation <i>Alt: Reeval. needs &amp; pgm promotion; deactivate Core</i>	-Documented increase in research project solicitation <i>Alt: Reeval program funding; Deactivate Core</i> - Documented benefit related to industry collaboration	-See note*
<b>Core</b>	<b>Year 01</b>	<b>Year 02</b>	<b>Year 03</b>	<b>Year 04</b>	<b>Year 05-10</b>

\*Note: Years 5-10- Intermediate and long-term outcomes that are outlined in the CTSI Strategic Plan and individual CTSI Core Program Descriptions that are developed during the Planning Phase will be achieved.