

The General Clinical Research Center (GCRC) and The Heartland Institute for Clinical and Translational Research (HICTR) at the University of Kansas Medical Center (KUMC)

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At last year's Merrill Research Retreat, we informed you of two major projects that would provide infrastructure for clinical and translational research at the University of Kansas Medical Center (KUMC). These two efforts are the General Clinical Research Center (GCRC) and the Heartland Institute for Clinical and Translational Research (HICTR). At this year's retreat, we provide an update on both of these.

General Clinical Research Center (GCRC)

A GCRC is an NIH-supported multidisciplinary research unit that facilitates investigator-initiated clinical studies and trials conducted by full-time faculty at an academic health center. GCRCs provide clinical research infrastructure to investigators who receive funding from federal agencies, private foundations, and other peer-reviewed sources. The space, equipment, and personnel of the GCRC are provided at no cost for investigator-initiated clinical research studies. The GCRC program has existed for nearly 50 years and is funded through the National Center for Research Resources (NCRR) of the NIH. Further information can be

found at their web site – www.ncrr.nih.gov.

We began the process of initiating a GCRC for the KUMC campus in 2002 and established four goals:

- Provide clinical investigators from the School of Medicine, School of Nursing and School of Allied health with a modern, state of the art facility in which clinical research could be conducted.
- Enhance multidisciplinary research across departments and the three schools.
- Enable and train junior faculty and trainees to become more involved in clinical research.
- Apply for federal funding to support the GCRC.

In January 2005 our GCRC became operational, and we began seeing subjects. In 2006, we applied for an NCRR/NIH grant, which was funded in April 2007 for \$7.5 million over three years. As of August 2007, we have approved 82 protocols that use the GCRC resources.

At KUMC, the GCRC is currently a predominantly outpatient unit located in approximately 6,000 square feet of newly remodeled space on the ground floor of the Delp Pavilion. There are six patient examination rooms; a large infusion / procedure area; a specimen processing laboratory; a cognitive testing room; a patient lounge; an exercise physiology suite with a metabolic cart; a metabolic kitchen; a computer laboratory; a conference room for GCRC and clinical research-related meetings; and administrative rooms for the biostatistician, nursing and administrative personnel, the program director, and associate and assistant program directors. With the beginning of grant funding, we now also can accommodate overnight patients in the University of Kansas Hospital through a scatter-bed system.

Additionally, with the NIH funding, three exciting new programs are now available to young researchers:

Clinical Research Feasibility Funds (CReFF) provide \$20,000 grants for pilot studies to young investigators (assistant professors or below). The proposed research project must use GCRC resources, and the applicants must first go through a protocol development process and meet with a senior investigative mentor, the research subject advocate, a biostatistician, and

the GCRC administrative director. We fund five CReFF awards annually, and the first five awardees were selected in July 2007. These first five CReFF awards at KUMC are:

- Jeffrey Burns, MD, Department of Neurology, Intranasal Insulin and Memory in Early Alzheimer's Disease
- Rajib Bhattacharya, MD, Department of Internal Medicine – Division of Endocrinology, Metabolism and Genetics Hypovitaminosis D and an Inadequate PTH Response in Chronic Liver Disease Patients
- Patricia Kluding, PT, PhD, Department of Physical Therapy and Rehabilitation Sciences, Pilot Project of Health Promotion for People with Diabetes
- In-Young Choi, PhD, Department of Neurology – Hoglund Brain Imaging Center, Hyperglycemia and Oxidative Stress in the Human Brain with Diabetes
- Andrea Ely, MD, Department of Internal Medicine – Division of General Medicine, Kansas Primary Care Weighs In II

Clinical Research Scholars Program (CRSP). This program allows a medical student to take one year off between years two and three or three and four to engage in clinical research. Students, with their mentor's advice, submit a protocol for a clinical research project. During the course of the year they complete the project under their mentor's tutelage. They also take approximately 12 hours of course work in clinical research, including the Introduction to Clinical Research course initiated in 2006 by Dr. Richard J. Barohn. CRSP students receive a stipend

of \$25,000. Three students were selected and began the CRSP program in July 2007:

- Kelsie A. Kropp / Mentor – Kathryn A. Ellerbeck, MD, Department of Pediatrics, Sex Differences in Autism: Potential Role of Oxytocin Signaling
- David C. Harmon / Mentor – K. Allen Greiner, MD, Department of Family Practice, Tailored Touch Screen Computers for Colorectal Cancer Prevention in Safety-net Clinics
- George P. Thomas, Jr. / Mentor – Jeffrey Burns, MD, Department of Neurology, Intranasal Insulin and Memory in Early Alzheimer's Disease

Summer Clinical Research Program for Medical Students. This program allows up to five students to work in the GCRC for eight weeks in the summer between years one and two. They are assigned to a mentor and become involved in their mentor's project. They present results of their summer research experience at the KUMC Student Research Forum the following spring. Summer medical students receive a \$1,400 stipend from the GCRC, which is partially matched by the medical school. The five students who participated in the GCRC Summer Clinical Program in June-July 2007 were:

- Janell Jones / Mentor – Patricia Kluding, PT, PhD, Department of Physical Therapy and Rehabilitation Sciences
- Jordan Roberts / Mentor – Patricia Kluding, PT, PhD, Department of Physical Therapy and Rehabilitation Sciences
- Willis Barrow / Mentor – Jeffrey Burns, MD, Department of Neurology

- Matthew Butler / Mentor – Richard Barohn, MD, and Yunxia Wang, MD, Department of Neurology
- Ryan Peck / Mentor – Jeffrey Burns, MD, Department of Neurology
- Anh Pham / Mentor – Richard Barohn, MD, and Mamatha Pasnoor, MD, Department of Neurology
- Luke Spencer-Gardner / Mentor Jeffrey Burns, MD, Department of Neurology

The Heartland Institute for Clinical and Translational Research (HICTR) and the Clinical and Translational Science Award (CTSA) Program

In October 2005, the NIH released a Request for Applications (RFA) announcement for institutional Clinical and Translational Science Awards (CTSA). Applications were due March 27, 2006. At that time, the NIH accepted two types of applications. The first was a one-time only planning grant application for \$150,000 to allow academic health centers time, and some resources, to further develop a full CTSA application. The second type was the full CTSA application that could be as large as \$6 million per year (if pediatric clinical research was involved and if the proposal included involving research in community settings; up to \$4 million without these components). In addition to the \$6 million per year, all existing NCI funded K30 programs for clinical research curriculum, NIH Roadmap clinical research K12 and T32 programs, and the long standing NCI funded GCRC grants are to be rolled into the CTSA application. By doing so, a full CTSA application could be awarded between \$8 and \$20 million annually for five years and become one of the largest

institutional research grants that an academic health center could receive. The NIH plans to fund 60 full CTSA grants by 2012.

The stated purpose for the CTSA project was to forge a transformative and integrative academic home for clinical and translational science, “to transform the local, regional and national environment for clinical and translational science, thereby increasing the efficiency and speed of clinical and translational research...by creating an academic home...that integrates clinical and translational science across multiple departments, schools, clinical and research institutions”. This new “home” in an academic health center must be a Center, Department, or Institute and must encompass all components of clinical research – including education, career development, and regulatory support components for clinical research infrastructure. These new clinical research units must promote multidisciplinary research teams, create an incubator for innovative research tools, and catalyze the application of new knowledge to clinical practice. Applicant organizations also must have degree-granting capabilities in clinical research that will lead a trainee to either a Masters or a Ph.D. degree in clinical research.

Shortly after the RFA was released, KUMC initiated a planning process to develop our response to this program. In March 2006, we submitted a planning grant which was funded in September

2006. With these funds we hired an operating manager and an administrative assistant. CTSA planning committees continued to meet, and a written plan was developed. In April 2007, Barbara Atkinson, MD, Executive Vice Chancellor and Dean of the School of Medicine, announced the formation of the Heartland Institute for Clinical and Translational Research with Richard J. Barohn, MD as Director and Lauren S. Aaronson, PhD, RN as Deputy Director. The HICTR is the infrastructure and vehicle for our CTSA application.

A Regional Approach to the HICTR

While the HICTR was established at KUMC, it extends beyond the walls of KUMC and the University of Kansas Hospital, bringing together several academic health centers and their affiliated hospitals and clinics (see Figure 1). This combined effort was created to nurture the next generation of clinical and translational investigators and to provide infrastructure support for innovative clinical and translational research in a way much greater than could be accomplished by its individual parts. Developing the HICTR in partnership with our colleague institutions on both sides of the state line also fits squarely within the broader vision of creating a major hub of Life Sciences research in the KC area.

With our partner institutions in the HICTR, we have developed a plan for training and supporting our next

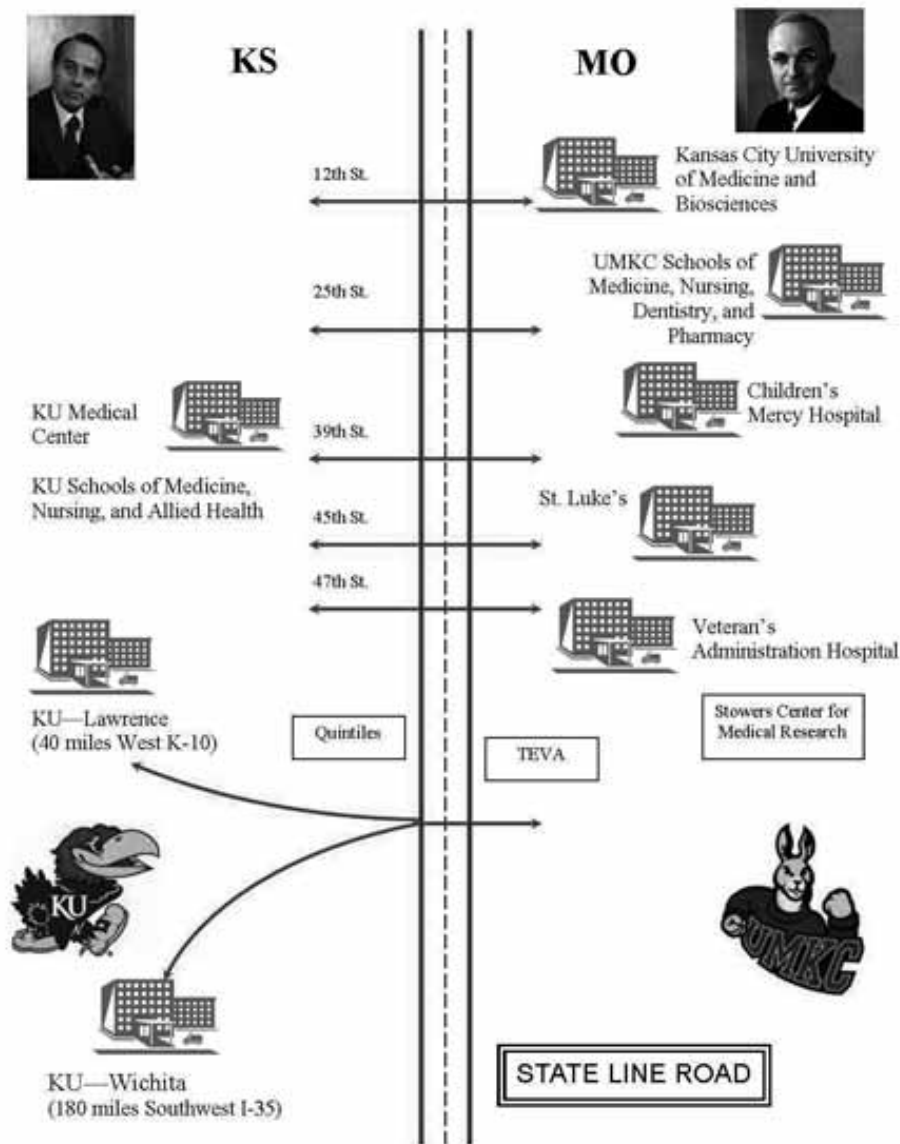


Figure 1. HICTR partnerships

generation of leaders in clinical and translational research and for providing health care scientists the tools to accomplish our unified goals through an infrastructure essential for moving clinical and translational research to new levels in our region. The HICTR is much more than an infrastructure vehicle for our CTSA application; it is a transformational, bridge-building entity that has quickly brought historically

competitive academic and community health care systems together under one virtual and physical roof. Coming at an auspicious time for the KC region, the creation of the HICTR builds upon other recent and exciting developments—including the formation of the Kansas City Area Life Sciences Institute (KCALSI), the Kansas Bioscience Authority, the Stowers Institute for Medical Research in Kansas City, MO,

and broad support of the governor, legislature, and public in Kansas for moving toward achieving a comprehensive cancer center at KUMC—backed by a \$5 million annual commitment in each of the past two years. All of these efforts have stimulated new levels of philanthropic support from the community and from business sectors for accelerating biomedical research in Kansas and the KC region. Community leaders and organizations have appreciated the unprecedented relationships developing between our health care systems and they are active partners in this transformative process. For example, in 2000 the Kauffman Foundation awarded a five-year, \$5 million grant to KUMC and Children’s Mercy Hospital (where UMKC pediatric faculty and researchers are located) to stimulate collaboration across the state line by awarding pilot and full program grants that required co-investigators from both sites. More recently, the KCALSI sought and obtained community contributions to award the HICTR a \$250,000 grant to launch our HICTR clinical research coordinator service. Private sector business enterprises, such as Quintiles, TEVA, Novartis, and Cerner, also have eagerly joined as HICTR partners and collaborators.

The new relationships we have forged are not only among the academic and affiliated health centers on both sides of the state line named in Figure 1, but also among a wide array of disciplines at each of our partnering institutions. Medicine, nursing, pharmacy, dentistry, allied health disciplines (such as physical therapy,

hearing and speech, dietetics and nutrition), public health disciplines (such as health services, epidemiology, and health economics), biostatistics, bioinformatics, bioengineering, psychology and sociology are all needed to address today’s major public health problems and all of these disciplines are active contributors to the HICTR. The multi- and inter- disciplinary collaborations currently active at KUMC and in the broader region will grow exponentially as we dramatically alter how we do clinical and translational research and open doors for wider collaboration. Through the HICTR, trainees from all campuses and from each of these disciplines will connect with each other, sharing educational and research experiences. And through the synergy created by the HICTR we envision enhanced opportunity to accomplish major advances in health and health care for all.

We believe the work done thus far to establish the HICTR at KUMC in partnership with our colleague institutions and the private sector in the Kansas City region position us to make unique and valuable contributions to the national CTSA consortium as set forth on the consortium webpage (<http://www.ctsaweb.org/>) with respect to:

- Encouraging the development of new methods and approaches to clinical and translational research
- Improving training and mentoring to ensure that new investigators can navigate the increasingly complex research system
- Designing new and improved clinical research informatics tools

- Assembling interdisciplinary teams that cover the complete spectrum of clinical and translational research
- Forging new partnerships with private and public health care organizations.

The HICTR vision, and penultimate goal, is to substantially add capacity for clinical and translational research in Kansas and the Kansas City region by revolutionizing such research through a dynamic partnership of university and academic health centers, major clinical facilities, community organizations, and private sector health industry entities in order to improve and enhance the health of all people. To do so, we set forth three central specific aims, which respond directly to the CTSA initiative:

- Dramatically increase the number of well-trained, multidisciplinary clinical and translational investigators in Kansas and the KC region through innovative and coordinated pre-doctoral, post-doctoral, and career-development educational programs in clinical and translational research;
- Dramatically increase the amount of cutting edge clinical and translational research in Kansas and the KC region through enhanced, creative, and coordinated infrastructure support from idea generation, proposal development and submission, through conduct,

implementation, and dissemination of the research; and

- Dramatically alter the way clinical and translational research is conducted to be more responsive to community health needs and to more rapidly bring research findings to the point of care.

The HICTR is the academic home for clinical and translational research at KUMC and in the Kansas City region. A conceptual representation of the HICTR is in Figure 2. The HICTR will provide the structure, knowledge, and support needed for a wide array of clinical and translational investigations, allowing investigators to focus on their science.

The central support unit, or hub, of our HICTR home is the Clinical Research Development Office (CReDO). The CReDO is where investigators go to initiate contact with any HICTR services and core support. The CReDO houses a clinical research coordinator pool and a comprehensive research grant development program; provides the investigator-friendly interface with all other components of the HICTR, including all regulatory program requirements, and all services and resources available to HICTR investigators; and is the formal administrative site for our Pilot Studies and Scientific Review Program, our Regulatory Support Program, and our Ethics Program. As such, the CReDO is the major coordinating unit for the entire HICTR.

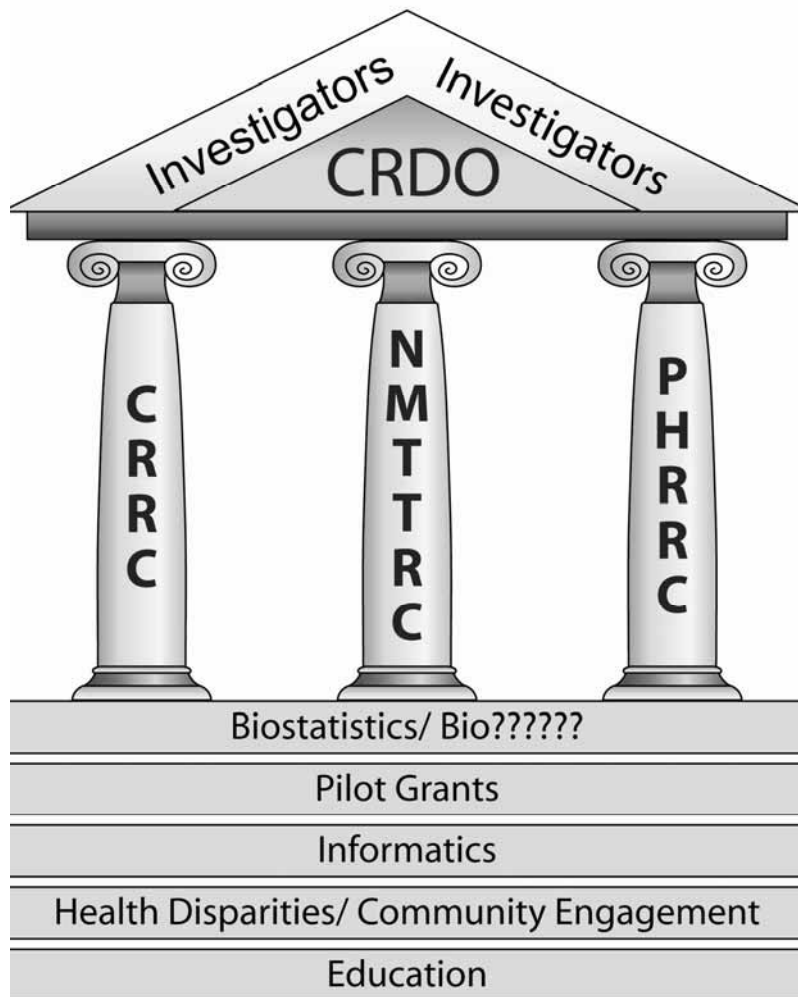


Figure 2. Schematic of HICTR. CRDO = Clinical Research Development Office; NMTRC = Novel Methods/Translational Technologies Resource Center; CRRC = Clinical Research Resource Center; PHRRC = Population Health Research Resource Center.

The three vertical pillars in Figure 2 represent the Novel Methods & Translational Technologies Resource Center (NM/TTRC), the Clinical Research Resource Center (CRRC), and the Population Health Research Resource Center (PHRRC). These resource centers are established to primarily support T1 (bench to bedside) research, clinical research conducted within the walls of dedicated clinical research units, and community-based and T2 (bedside to practice) research,

respectively. However, walls between these resource centers are permeable in order to support the considerable interaction that occurs as research moves from the bench through trials and other investigations with humans and on to implementation and dissemination in practice, and as ideas flow back again from all points along this continuum as experiences and discoveries give rise to new needs for investigation. Figure 3 depicts our conceptualization of this research process and the feedback loops.

The HICTR Research Conceptualization

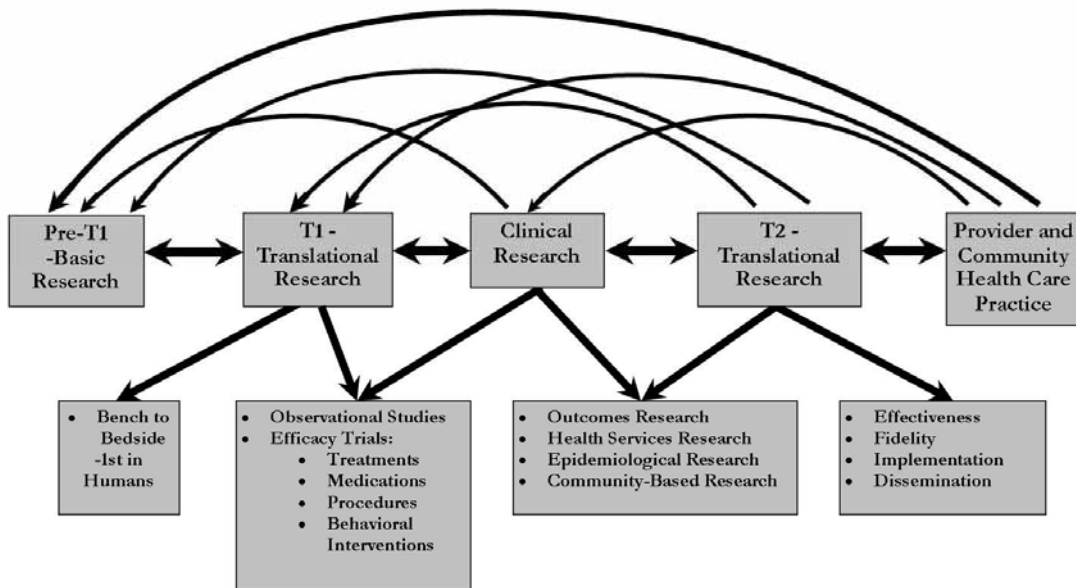


Figure 3. HICTR Research Conceptualization

As shown in Figure 3, not only is there feedback between adjacent boxes, but feedback from any location may go directly back to any other point along the continuum, depending on the idea underlying the feedback and the nature of the research needed to address the identified need. For example, in the process of implementing a new treatment, questions may arise that would stimulate new research needed at the bench, perhaps with respect to identification of new genetic markers. Or, community needs identified through the activities of our Community Engagement Program may generate research questions that must be addressed first at the bench level.

As shown in Figure 3, T1 research (defined in the CTSA RFA as “applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans”) involves studies characterized as first in human explorations drawing on evidence initially obtained at the bench. Clinical research includes observational studies as well as traditional clinical trials of treatments, medications, procedures and behavioral interventions. Depending on the nature of a particular study, outcomes research, health services research, epidemiological research and community-based research also may be characterized as clinical research (still in the discovery phase). When such

research focuses on actual translation into practice, including issues of the cost-effectiveness of prevention and treatment strategies, it falls under the T2 research rubric (defined in the CTSA RFA as “research aimed at enhancing the adoption of best practices in the community”). Purely T2 research is best characterized as studies concerned with effectiveness, fidelity, implementation, and dissemination.

While the CReDO serves as the unifying and coordinating hub to ensure this dynamic interaction among all investigators and across all types of clinical and translational research, our three major resource centers have been established to each focus on discrete types of resources and the expertise needed to use these resources for T1 research, clinical research conducted within the walls of dedicated clinical research units, and community-based and T2 research. As such, the NM/TTRC includes cores for in vivo imaging, disease models and assessment, cell and tissue imaging, and biomarker and molecular interrogation.

The CRRC includes the GCRC at KUMC, the NIH funded Pediatric Pharmacology Resource Unit (PPRU) at Children’s Mercy Hospital, the Clinical Trials Unit (CTU) at the Kansas City University of Medicine and Biosciences (KCUMB), the Clinical Research Institute (CRI) at the KU SOM in Wichita, and the clinical research facilities at Quintiles, a large private clinical research organization with which KUMC and the HICTR is partnering. The PHRRC provides a wide array of support services for clinical and translational research projects not provided through

the NM/TTRC or the CRRC, including issues and activities related to accessing participants for research and working with communities and community providers, and houses the HICTR Community Engagement Program and Health Disparities Research Support Program. The PHRRC also will house and support use of large national research databases, such as the NHANES, and will maintain a repository of clinical research assessment tools, such as those recommended by the NIH Patient Reported Outcome Measurement Information System (PROMIS) collaborators.

To provide the full complement of resources needed to support the training and education of clinical and translational investigators and to support the generation of new clinical and translational research, the HICTR also includes a dynamic Clinical and Translational Research Education Center (CTREC), which administers a pre-doctoral T32 program, a post doctoral K12 program, and numerous other educational and training programs including mentor training and support and a clinical research coordinator certificate training program. And, the HICTR will support and provide biostatistics and informatics support and collaboration through the Center for Biostatistics and Advanced Informatics and through the Center for Healthcare Informatics.

Current Status of the National CTSA program:

In September 2006, when we were notified of the funding of our CTSA planning grant, the NIH also announced 51

considerable delays in getting new treatments and other findings from clinical research into practice so that the public realizes benefits from these new discoveries. Recognition of the need to extend collaborations across many disciplines within and outside of medicine came from acknowledgement that today's health problems require the contributions of a wide range of disciplines, including bioengineering, epidemiology, nursing, public health, statistics, informatics technology, sociology, and many others.

The CTSA program already has stimulated major changes in how clinical and translational research is conducted

at academic health centers competing for these coveted awards. Because of the importance of this relatively new initiative, the NIH CTSA program has been established under a cooperative agreement mechanism, and the NIH is actively involved with all funded CTSA programs, including with respect to a national evaluation effort and other activities involving collaborative efforts across funded CTSA sites. The ultimate goal of the CTSA program is to see that the public's health is improved through more rapidly transferring results from increasing amounts of clinical research to actual health care practice.