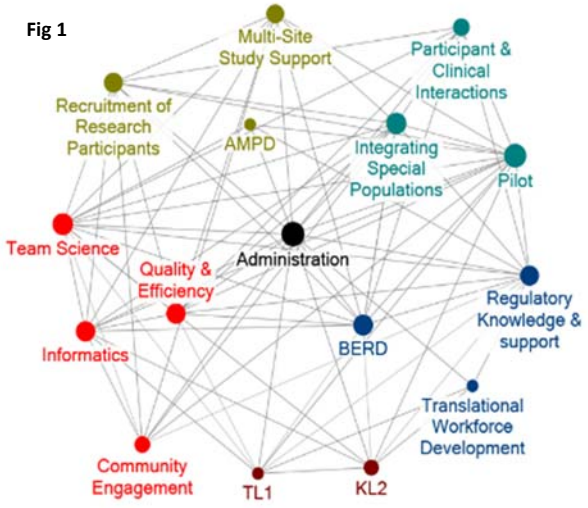
COMPONENT 1. OVERALL RESEARCH STRATEGY. **LEAD: REZA SHAKER, MD**

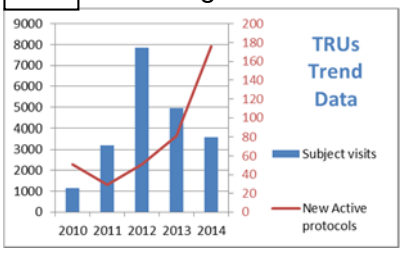
Significance and Background: As evidenced by the state-of-health in our nation and world-wide, the current approaches for improving health are slow, expensive and inadequate to meet the current and future needs. These shortcomings only can be addressed by identifying and adopting innovative mechanisms to efficiently translate discoveries emanating from the bench, the clinic or the community into preventive, diagnostic and therapeutic interventions that more rapidly benefit patients and help improve human health. Fundamental to the success of this transformative approach is the availability of a well-trained translational work force and the meaningful engagement of a community of stakeholders collaborating across all related segments of society. Therefore, we propose three overarching specific aims as stated above, which incorporate the eight components and their associated modules described in the current FOA, in order to achieve our ultimate **Vision,** to advance the health of our community and our nation through research and discovery and our **Mission,** to develop the Southeast Wisconsin CTSI (CTSA 1.0) into an integrated, shared home for clinical and translational research and research training, hallmarked by a borderless, collaborative, synergistic and investigator/community/patient-friendly research environment that is functionally integrated into regional and national CTSA networks (CTSI 2.0), with the overarching **Goal** of "enhancing the transit of therapeutic, diagnostic, and preventive interventions along the developmental pipeline." As seen in the table on the Specific Aims page, the FOA's various components and modules map onto one or more of our proposed specific aims in a pattern that has been designed to reflect the strengths and needs of our CTSA hub. It demonstrates how these components come together to construct our translational engine and what component of the engine they constitute. Figure 1 illustrates the collaborative relationship among these modules. Lines indicate collaboration between modules; the size of the circles correspond to the number of collaborations in which a given module is involved. Each of the FOA's eight components will be discussed in the subsequent sections with references to their relationship and contribution to our proposed specific aims, how we plan to achieve the proscribed goals set forth for each component, and how we will evaluate and parameterize the success by presenting appropriate metrics. **Our Principle of Operation** in these and all collaborations will be "complementation and synergy and avoiding duplication, in order to achieve better outcomes faster and more cost effectively."

Fig 1



The backbone for the proposed implementation of this next phase of our CTSI development (CTSA 2.0) is 1) inspired by the recent IOM report and the current FOA, 2) shaped by five years of successful operationalization and outcomes of our CTSA1.0, and 3) aligned with a comprehensive blueprint of our regional strategic planning (in 2014), which incorporates the lessons learned by more than 400 participating stakeholders representing academic institutions, health care systems, industry, patient advocacy groups and citizens.

Fig 2



Although Translational Research Units (TRUs) are not included in the current FOA, our adult, pediatric and veteran/geriatric translational units have been important contributors to the work and success of our investigators and perform a crucial function and have been consistently used by a large number of our investigators (Figure 2). They have been funded by our institutional resources in the last five years and will be funded by the same braided funding stream for the next five years. Therefore we have included the TRUs in this proposal without any cost to the grant as noted in our matrix budget.

Innovation: Our overall proposal and its various components feature many innovative elements; only a few can be highlighted here due to space limitations. Each helps constitute the fabric of our current CTSI hub and establishes the framework to achieve the next level in our development:

1. The unprecedented collective commitment and collaboration of four independent degree granting academic institutions, three health care enterprises and two research institutes in southeast Wisconsin

to advancing translational and clinical research in the region by partnering in the creation and continued support of the Clinical and Translational Science Institute of Southeast Wisconsin,
2. A novel multi-institutional governance structure with a successful five-year track record of participative leadership with authority over budget and space,
3. The creation of mutually learning Healthcare Enterprise-CTSA- Eco-System,
4. A track record and updated plan for collaborating in regional and national CTSA networks,
5. Borderless research facilities and seamless support services accessible to all partnering faculty comprising medical and non-medical disciplines as well as community investigators in the region,
6. Expanded facility and services of age specific Translational Research units (TRUs) to serve adult, pediatric, geriatric/veterans, and under-represented diversity populations, which are complemented by a mobile research unit to reach those with special needs or problems accessing the TRUs,
7. The development and completion of the Southeast Wisconsin Biomedical Informatics Connectome (BIC), which includes Web-based communication and collaboration tools; robust integrated clinical database platforms and biomedical informatics support; data-warehouses; Clinical Trial Office resources; community/patient connectivity; translational resources and services and a Faculty Collaboration Database (2,300 profiles with contact information), all accessible through our hub`s digital portal/website and connected to our in-house developed data tracking/management system (Waypoint),
8. Coordinated intra- and inter-institutional granting mechanisms to nucleate research teams and stimulate inter- and trans-disciplinary research that promotes team science and community engagement,
9. Regional *One City-One IRB* and statewide IRB Reliance Agreement mechanisms along with development of training modules for IRB membership to improve quality and novel processes to accelerated review,
10. Availability of a continuum of clinical/translational research education/training opportunities and mentoring for diverse individuals at varied stages of research career development.
11. Mechanisms to improve investigator education/training and access for private/public partnership and commercialization processes (AMPD optional module),
12. A firm commitment and well-designed plan to attain and maintain efficiency in IRB-related processes and promote the ethical conduct of clinical and translational research through integration, linkage and facilitation of ethics education, consultation, regulatory and professional development activities,
13. A robust mechanism to a) engage stakeholder Communities as partners and contributors in translational research and b) train/mentor our investigators in working with communities on their research and thereby complete the continuum of clinical and translational research participation,
14. A novel mechanism for inter-CTSA collaboration and complementation for research training through our proposed “Translational Training/Education Collaboratory (TTEC)” along with distance learning programs in team building and team science,
15. Strong operational mechanisms for promoting collaborative and trans-disciplinary research teams through education (MS, PhD, K12 and clinical scholars program), facilitation (multi-disciplinary grand rounds, informal gatherings via “Science Club,” faculty databases, and nucleation through our pilot grants funding),
16. An operational six-CTSA consortium for the conduct of multi-site clinical trials (MARCH),
17. Development of our recently launched Clinical Trial Office (CTO) into a regional CTO supported by our hub partners, and
18. A robust mechanism for synergy and leveraging of community engaged programs of our hub partners and community health charities comprised of 75 organizations, along with catalyzing CTSA programs, which involve and garner input from a community of stakeholders in need identification, concept development, advice and consultation opportunities and participation in funding decision processes associated with the conduct of translational research.

I. Vision and Strategic Goal for *Workforce Development* We are committed to developing a diverse translational workforce, well trained in team science and translational/ clinical research, capable of engaging the community of stakeholders in various aspects of their research through a multi-pronged approach, including our KL2, TL1, degree and non-degree programs.

1. Curriculum. We have adopted a six--pronged approach to train and educate a robust and diverse translational work force and to prepare research teams with the skills and knowledge needed to advance the

translation of discoveries. These include existing(1-4) and new programs: 1) Training research-intensive Translationalists through the KL2 program, which essentially prepares the next generation of leaders for team science, 2) A two year Clinical Scholars Program that will equip at minimum the clinicians from a diverse discipline with the knowledge and skills needed to conduct translational research and participate in team science, 3) a Master's Degree in Translational Sciences with focus on Team Science that will prepare clinicians and non-clinicians to engage in translational research, 4) two Ph.D. degrees, one with focused training to prepare basic science PhD students for engaging in translational research and the other a PhD in translational rehabilitation at our partner institution, Marquette University, 5) A number of training modules and non-credit courses in principles and methods of community engagement and clinical and translational research for faculty and staff, and 6) a TL1 pipeline program.

As described later in the workforce development module, we have expanded our non-degree training programs in order to leverage the expertise present among our partner institutions' faculty to offer more training modules in various aspects of clinical and translational research and community engagement. As important, we propose to develop a "Translational Training/Education Collaboratory" (TTEC) taking advantage of our existing collaborative relationship with five other CTSAs members of our MARCH consortium described later (see letters of support) to complement each other's training programs and jointly develop new ones needed to avoid redundancy and duplication. We will coordinate this effort with the National Education Domain Task Force to avoid duplication. Indeed, TTEC can potentially become an effective, complementing collaborator to help realize the goals of the task force.

Training in Collaboration, teamwork and team science. As stated in the current FOA, translational research is essentially a team science. The ability to network and engage in collaboration and team work does not come naturally to most people despite their scientific qualifications. As described in the workforce development module as well as the KL2 and TL1 programs, we plan to leverage digital media to offer a number of resources and training courses in networking and team building not available in our hub through collaboration with other CTSAs. In addition to "TTEC," we have developed an agreement with the Harvard University CTSA to provide our colleagues access to their educational resources/ symposia designed for this purpose (see letter of support). This will further prevent duplication and redundancy.

Training in community engagement. Our training plan includes programs aimed at equipping our translational work force with the knowledge and skills to engage the community of stakeholders appropriately in the translational process. We build on our long institutional history of community engagement and our CTSA`s community engagement training and consultation core as part of our existing and future training programs.

Training of clinical practitioners. Our experience over the past five years suggests that participation of front-line practitioners in research is enhanced by understanding and buy-in of how translational research can improve patient care as well as positively impact upon job satisfaction and the sense of achievement of the caregivers themselves. To address this issue, we will develop in collaboration with "TTEC" and offer a "Translational Research Learning Module" for clinicians to be included in the professional development program for our physicians, nurses and other clinical groups. We believe this approach also will help inculcate a culture of valuing, supporting and engaging in translational and clinical research in clinical practice.

Opportunities and challenges in improving clinical and translational research and training. With the establishment of our CTSI 1.0 in 2010, clinical and translational research has gained significant recognition among our faculty, who have taken advantage of the support and services and infrastructures such as TRUs and pilot awards as well as translational education/training programs. Taking advantage of a dedicated funding stream (from our clinical practice, MCP), in the past two years our clinicians have begun to **Integrate Research Into Clinical Practices (IRICP grant)** by formulating testable hypotheses inspired by their clinical experience to address commonly encountered clinical challenges. An example of these projects is provided in the insert box above. Our clinical practice group (MCP) has contributed over $125K annually to support this initiative and pledges to do so for the next five years. So far 34 teams have competed for these awards ($15-20K) and 14 have been funded. This is in addition to NIH-supported and our institutional pilot awards provided by our partner (MCW) institutional

Dr. Josh Field, a young investigator appointed jointly at MCW and BRI, was awarded IRICP grant to test his clinically-based hypothesis about high prevalence of psychological abnormalities as a contributory factor in frequent ER/hospital visit by sickle cell disease patients. His study showed that 62% met the criteria for psychiatric referral, based on the Millon Behavioral Medical Diagnostic. This approach is being adopted by our health system, and a manuscript is being published.

resources, totaling over $700K/year, which supports between 12-14 teams annually. However, significant challenges remain that prevent us from fully capitalizing on the substantial talents of our multi-institutional faculty through their participation in team science. Most notably is the limited time available to clinician scientists to properly balance their research activity and their clinical duties. A number of plans have been implemented to lessen this burden, including providing 70% protected time for our NIH KL2 and institutional KL2-equivalent scholars, 30% protected time for our clinical scholars and time release plus department paid tuition for MS students. MCW centers of excellence, including Cancer Center, Digestive Disease Center, Cardiovascular Center and the Imaging Research/Neuroscience Centers, all offer pilot awards annually and have agreed to coordinate these awards with CTSI, allocating a portion of these funds to Translational projects in their own field. More important, they have agreed to allow 10% of salary support for the PI of their respective projects while the department of the PI is expected to match an additional 10% protected time. These will allow for 20% protected time for an additional 15-20 investigators per year. Each MCW clinician faculty also is granted 2 half days for academic/scholarly pursuits, further supplementing our PIs' protected time for conducting their research. Despite significant improvement, a continuing challenge is inadequate knowledge about available resources and supports for CT research. We believe these challenges can be remedied by our biomedical informatics connectome capabilities and proposed TRIAD service described later.

2. Diversity participation in clinical and translational careers. Despite significant continued efforts to increase diversity participation in research careers, our hub remains behind in our expected goals. Southeast Wisconsin is the urban center of the state with nearly 2 million people living in Milwaukee and its sister cities along the eastern shore of the Lake Michigan. It enjoys one of the most diverse and vibrant religious, cultural and racial heritage in the state. As seen in **Table 1**, our average multi-institutional representation of diversity groups falls below the regional diversity statistics. Dr. Dawn Bragg, MCW's Associate Dean for Student Affairs-Diversity, who possesses extensive experience in minority recruitment/retention, has been recruited to our CTSA hub to spearhead our efforts and to track subsequent activities in this regard. These will include formation of a Regional Translational Workforce Diversity Committee (RTWDC) comprised of leaders of our partner institution`s diversity initiative/offices, including Dr. Cheryl Ajirotutu, Associate Vice Chancellor, Global Inclusion and Engagement -UWM, Dr. Al Walker, Senior Associate Dean for Diversity-MCW, Dr. William Welburn, Associate Provost for Diversity and Inclusion-MU, Dr. Tom Bray, Dean of Research-MSOE), and more important, representatives from under-represented minorities, Dr. Bevan Baker, City of Milwaukee Commissioner of Health-African-American Community, Dr. Thelma M. Newby, Set Ministries, Ana Paula Soares-Lynch, Proyecto Salud Director, CORE/El Centro-Hispanic Community, Lisa Anderson, MS, American Indian Community Outreach Coordinator, as well as Dr. Veronica Flood, Chair, MCW's Women's Faculty Council, to advise and assist us in these important efforts. We also have devised a clear evaluation and tracking plan for the next ten years to monitor progress.

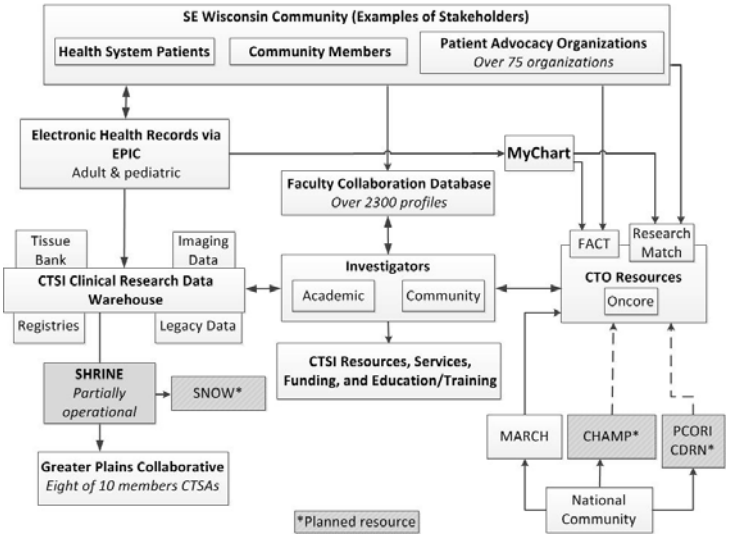
TABLE 1.	Women	White	African American	Hispanic	Asian	Native American
11 County S.E. Wisconsin Region	50%	84%	7%	7%	3%	1%
2 Counties of our hub facilities	51%	72%	14%	9%	3%	1%
CTSA Hub	35%	82%	3%	2%	12%	1%

3. Collaboration with other CTSA hubs. In establishing an inter-institutional research environment based on the principles of collaboration, complementation, facilitation and education, our CTSI is well positioned to elevate its development to the next level in concert with NCATS (CTSA 2.0) vision, "to improve the translational process to bring more new treatments to more patients more efficiently and to enhance the NCATS program capacity through development of national networks and support of multi-site research." Indeed, our CTSI embraced this broader vision during the last funding period by being one of the founding members (see letter of support) in forging a multi-CTSA consortium including: UW-Madison, Mayo Clinic, Indiana University, University of Minnesota and Ohio State University to facilitate and conduct multi-site research. This multi-CTSA consortium, commonly known as "MARCH" (Midwest Area Research Consortium for Health), has enlarged our scientific community. Through MARCH, we have successfully built an effective infrastructure, which now provides an established base for regional research efforts, dedicated to creating efficient and effective clinical trials by minimizing duplication, standardizing data capture and reporting, and improving multisite study performance through best practice methodologies. This has included establishing: 1) a comprehensive marketing portfolio; 2) standard operating procedures; 3) a specialized governance structure incorporating a multitude of personnel from ancillary service areas; 4) mechanisms to ensure effective and efficient regulatory and contract review through reliance agreements and master agreements; and 5) proven communication approaches for use across our geographically dispersed sites. MARCH has seven currently

active studies crossing foundation, federal and industry sponsorship, ten trials pending federal and industry funding, and two industry partnerships. Indeed, MARCH is becoming a national model for other consortia. This valuable experience has provided us with the knowledge and the know-how to be an effective participant and a leaders in the national network of CTSAs envisioned by NCATS.

Building upon the working relationship among the members of this consortium, we have now laid the ground work to collectively develop a "**Translational Education/Training Collaboratory-TTEC**." The goal of this Collaboratory is to create a comprehensive inventory of all our training programs and make this inventory accessible to investigators across all six MARCH CTSA hubs. We anticipate sharing our unique programs by an effective and efficient means, including but not limited to, video conferencing for live participation, videotaping for delayed use, or other potentially suitable methods. When appropriate, participants in "shared" courses can, if possible, obtain credits for their efforts or simply audit the offerings. We have agreed to dedicate necessary resources for the developmental effort. We will constitute a steering committee comprised of the respective education and training leaders of our hubs in early 2015 to operationalize the Collaboratory. This collaboration will not be limited to the Midwest and gradually will include other interested CTSAs. Furthermore we have joined the Child Health Research Through Multisite Planning consortium (CHAMP), led by Irvine and Children National/George Washington CTSAs) as our multi-site study project to specifically contribute to advancing child health. It is noteworthy that MARCH itself has been instrumental in advancing child health in the Midwest by facilitating and managing pediatric trials including a pediatric leukemia multicenter trial (its first) among others.

Figure 3 **Biomedical Informatics Connectome (BIC)**



B. Vision and strategic goals for creating a shared environment within hub and CTSA network. Since its inception in 2007 and accelerated by the acquisition of the NIH CTSA grant in 2010 (CTSA 1.0) and matching institutional funding, the resulting Southeast Wisconsin Clinical and Translational Science Institute (CTSA1.0) has been gradually woven into the fabric of our partner institutions as the recognized shared platform for meaningful collaboration and high quality team science in our region. What started five years ago as a southeast Wisconsin "experiment" among community institutions has emerged as a successful southeast Wisconsin functional enterprise that has deeply influenced the transformation of our biomedical research programs and upon which CTSA 2.0 will be founded to continue solidifying and expanding our borderless research environment. In CTSA 2.0 our shared environment not only includes investigators who can advance their research and training by benefiting from the collective resources and services of our hub and parent institutions, but also includes the community of stakeholders that can effectively (as described in CE Module) participate, contribute and benefit from this shared environment. The Biomedical Informatics Connectome (BIC, Figure 3) is the backbone of this shared environment. BIC is accessible through our digital portal/website and provides personalized concierge services though TRIAD, as described in subsequent components. Several examples of our achievements in developing and facilitating a shared environment and accomplishments of our researchers supported by this environment are provided later.

TABLE 2	2010	2011	2012	2013	2014
# Multi-disciplinary Teams	8	17	19	23	20
# Team Members	24	52	60	89	67

How to increase incentives for teamwork, facilitate the assembly of multi-disciplinary translational team and promote collaboration*:*

We have devised and implemented several mechanisms to encourage and facilitate teamwork:

Allison A. Hyngstrom, PT, PhD, an MU faculty received a NIH-KL2 Award in 2011. Her research topic was central mechanism of neuromuscular fatigue after stroke. She extended her work through CTSI Pilot grants. Her CTSI-supported studies resulted in an NIH-R21 (3rd percentile). Her R15 on a similar topic has scored at the 9th percentile.

1) Through our nucleating pilot awards. A fundamental requirement for a proposal to receive funding through our pilot award mechanism has been and will continue to be its multi-disciplinary and multi-institutional nature. Over the past five years, the culture of team work and team science has expanded and

strengthened its roots in our institutions. **Table 2** shows the number of research teams formed and successfully competed for our nucleating pilot awards and the total number of team members. These teams have collectively presented over 200 presentations in national and international meetings, published 47 papers and produced 2.7:1 ROI in grant funding.

2) Team work and team science are also taught in our MS degree courses, clinical scholars program, NIH supported KL2 and institution supported KL2-equivalent programs in our hub. Several examples of how investigators have successfully used these opportunities are presented in the insert boxes.

As described later in this proposal, teamwork and team science will continue to be the central theme of our education/training and will be encouraged and supported by our nucleating grant support and research resources over next five years as we implement additional plans to solidify research teamwork and team science in our institutions. These will include: a) additional positive points in promotion and evaluation by our MCW's Rank and Tenure committee for participation in team science (as supported by a letter from Director/P.I. of our CTSA hub), b) additional points for receiving annual incentive for participation in team science (as supported by a letter from Director/P.I. of our CTSA, c) eligibility for the Dean`s Award for Translational Sciences instituted in 2014, which carries a $5,000 cash prize (Dr. Mary Horowitz, a translational researchers in Hematology/oncology/bone marrow transplantation was the first recipient of this award, d) nucleating workshops (described later in related component)) which brings multi-disciplinary scientists and various communities of stakeholders together to identify and help develop translational research projects to compete for nucleating pilot feasibility funding, and e) by use of the "Concept Development Assistance" process through our TRIAD (described later).

The results from **Dr. John Baker's CTSA pilot grant** showed that a probiotic bacterium, *Lactobacillus plantarum* increased flow-mediated dilation and decreased LDL-cholesterol in patients with established cardiovascular disease. Dr. Baker has now shown this probiotic decreases myocardial infarct size in rats. These findings formed the basis of a US patent application, "Methods for diagnosing and treating cardiac defects." US patent application 20130052172 Baker; John Edward February 28, 2013

Our CTSA TRU and BioStats supported **Dr. Reza Shaker's project** on pathophysiology of upper esophageal sphincter (UES) in patients suffering from aspiration of gastric content. These studies resulted in development of: a "UES Assist Device" to prevent aspiration, which underwent IP/commercialization process, followed by completion of a successful pivotal FDA trial, showing 87% efficacy. Final clearance is imminent. US patent application WO2014/186500AZ (2011)

The findings of CTSI Pilot Awardee, Dr. Violet Bumah, (UWM Health Sciences) indicate that the bactericidal effect of blue light can be optimized to yield 100% bacterial clearance, potentially benefiting human cases of severe topical MRSA infection. A commercial protocol currently under development could be used to eradicate Methicillin resistant Staphylococcus aureus in various environments that harbor the MRSA bacteria.

Dr. Mahsa Ranji (UWM-Electrical Engineering faculty) , A CTSA NIH KL2 recipient and CTSA pilot awardee received a Patent based on her CTSA supported project for In vivo Measurement of Mitochondrial Function (US patent 8473036, June 2013).

Anand Padmanabhan MD, a junior investigator at MCW/BRI received CTSI pilot grants in 2012 and 2014 to study the pathophysiology of Heparin induced thrombocytopenia (HIT), that affects 1-5% of patients treated with heparin. These studies resulted in development of a novel method to differentiate pathogenic from non-pathogenic HIT antibodies, a distinction that is hard to make with current diagnostic testing. Anand is in the process of bringing this improvement to the patients (PCT/US14/62591; Oct, 2014).

The usefulness, outcome and impact of these approaches will be systematically evaluated on an annual basis using evaluation/tracking methods described in following sections. These findings and potential needs for change will be shared with the relevant parties in a timely manner. Our evaluation team has actively participated in the regional and national CTSA evaluation group, which will be an effective conduit for sharing experience, collaboration and dissemination of new research tools and methods that will be developed by our science teams. In 2013, our CTSA participated with 12 other CTSAs in the national common metrics workshop, which provided critical lessons about the feasibility of collecting and utilizing common metrics at our and other CTSA hubs. (Rubio, Doris McGartland "common metrics to access the efficiency of clinical research) evaluation and the health professions. August 2013:36; 432). More recently, our evaluation team is working with four other CTSAs to develop a "translational algorithm" using a machine learning approach. The ultimate goal is to automate the categorization of research and publications along the translational continuum (T0- T4) so that we can better evaluate our strategies to move research bi-directionally across the continuum.

C. Our vision for engaging local and national communities in all phases of translational research. *How do we increase engagement of interdependent stakeholders?* Data [1,2] suggests that most Americans value healthcare research, but many do not believe it works in *their* interest, and most believe it is the purview of technical experts – not a shared societal undertaking. In fact, guidance and collaboration with engaged non-researchers is recognized as a key to ensuring first that researchers address questions that matter and second that researchers successfully carry out the studies that will answer the questions. Thus, we believe that a key requirement for our CTSA hub's success is to engage the creativity and resources of the broader population in

the service of research and discovery for health. As our CTSI moves into its second five years, we are focused on identifying and implementing innovative mechanisms to build on our current successes in this area. We have designed a two-pronged model.

The first prong offers a general approach aimed at educating/informing the public in southeast Wisconsin about importance of translational research worthy of their support and engagement through the use of mass media. For instance, we have broadcasted a radio program for the past year with coverage of 30,000 listeners in southeast Wisconsin along with podcasting and live streaming. This approach has a strong potential for regional or national collaboration to educate and gain the trust and support of the masses for advancing health through translational research. Notably, we do not advocate purchasing air time, but instead have persuaded the radio station WMSE 91.7 FM (a subsidiary of our partner; MSOE) to donate the time to CTSI. Our CTSI communication staff conducts the interviews and produces this simple program. Similar opportunities are being explored at our partner UWM for using their local affiliate of National Public Radio. We will in the next five years expand this program to regional Hispanic, African American and American Indian radio stations, all supported by non-CTSA funds provided by our partner institutions and through MCW's Public Affairs Office. Through the airwaves and digital media, we plan to win the hearts and minds of our citizens to consider research and discovery as an important civic duty worthy of their support.
Our model also focuses on forging close partnerships with community and faith-based organizations to build broad acceptance of the view that participation in research and discovery for advancing health is a fundamentally virtuous activity, similar to environmentally sound use of resources. We plan to pursue this approach through formation of various councils targeting under-represented groups.

The second prong of our model (detailed in the community engagement module) is designed to engage communities of stakeholders in all phases of translational research and to increase engagement of interdependent stakeholders such as patients, clinicians, healthcare delivery systems, government agencies, and industry.

D. Vision for how to incorporate where possible translational research across the lifespan.
Our Hub is fortunate to include Children's Hospital of Wisconsin (CHW), one of the foremost children's research-oriented health systems that has consistently ranked among the top ten best children's hospitals in the nation. CHW supports a research institute (CRI) for the past ten years with an annual budget of over $10 Million. MCW faculty staff the hospital and constitute the CRI researchers. Dr. Calvin Williams, the CRI Director is a CTSI Executive Committee member and a co-PI on this grant. The CEO of CHW is a member of the CTSI Board of Directors (BOD), the highest administrative body of our hub. The CTSA PI reports to the BOD and the Dean of MCW, who chairs the BOD.

Our CTSA hub is deeply committed to pediatric research. CTSI and CRI co-manage our pediatric TRU, which has been and will continue to be fully funded by our Children's Hospital for the next five years, and currently supports101 active projects. Since 2009, our CTSI has supported 22 pediatric research projects ($1.1 Million) through our nucleating pilot feasibility grants and directly supported the education and training of 49 Pediatrician scientists (21 Clinical Research Scholars,1 KL2 and 28 MS degrees). To further support pediatric research, our hub has joined eighteen other CTSAs to form a nationwide collaborative consortium for child health research, "CHAMP" discussed previously. Our hub also is fortunate to partner with the Zablocki VA Medical Center (ZVAMC), a regional referral center for our veterans. ZVAMC and CTSI have uniquely collaborated to use institutional resources to develop and operate a TRU located on the fifth floor of the hospital for the past five years. This unit has been the site of all studies related to the "One Million Veteran" project, in addition to 15 research projects currently addressing veteran related health issues. This arrangement allows our investigators to engage in both aged-related research, and, as important, translational investigations particularly related to disabled veterans. Investigators from ZVAMC and our partners MSOE, MU and UWM collaborate frequently on rehabilitation projects and device development for improving the functionality of disabled veterans

E. Vision and strategic goals for improving and streamlining methods and processes with focus on quality. Operationally, translational research not only depends on researchers and their team members, but also on the personnel, who provide critical administrative support behind the scenes to process contracts, manage purchases, support institutional review boards and maintain the infrastructures needed for the conduct

of research. Although in different ways, the skills and efficiency of both groups are important in order for the CTSA hubs and NCATS to achieve their goals.

With quality and efficiency of processes as a focus of this FOA, this is a timely opportunity to introduce the LEAN culture into our southeast Wisconsin clinical and translational research enterprise, particularly in an era of shrinking resources and cost containment. Similar programs have been utilized in clinical enterprises and have produced significant improvements in increased value and efficiency (ref), but these methods have not been employed commonly in management of research operations. We are fortunate that one of our partner institutions, MSOE has a long standing track record on this topic and has provided these services to industry for many years. MSOE and MCW have recently collaborated in developing a joint program that embeds MSOE industrial engineering students under the supervision of program faculty into the MCW adult practice group to help implement process improvement and change management. As described in the Quality and Efficiency module, we will incorporate LEAN into all aspects of our CTSI and research infrastructure as an aid to understanding and minimizing roadblocks, and also recognizing and remedying potential gaps.

In addition, for the past four years we have used quantitative and qualitative methods, such as logic models and data collection plans to systematically collect, track and evaluate metrics across our programs and services. Using data collected over time, we have appropriately modified some of our programs, services and initiatives leading to new initiatives such as **the nucleating workshops**. Our approach was first piloted in December 2013; evaluation data indicated 4 multi-disciplinary teams were formed and are actively pursuing research and funding in the area of women's health (see more in Team Science section). The evaluation team also analyzed and presented data on investigators utilizing and benefiting from CTSI services in 2013. Based on the results, CTSI leadership formulated strategies to disseminate information about CTSI resources and support to partner institutions, tailored to their institutional culture and dissemination structures and methods. They also brainstormed incentives and tools to better connect investigators to the myriad of services and support CTSI has to offer. This approach will continue in the current proposal. To improve reporting, tracking and evaluation efficiency, we have completed phase 1 of the development of an in-house electronic tracking system named "Waypoint." Beta testing was successfully completed, and we have begun data input. This system is planned to be operationalized to full capacity in the first year of this proposal. All common metrics will be captured in Waypoint (see more in Evaluation section).

As mentioned, our evaluation personnel have been collaborating with four other CTSAs including UW-Madison, NYU, Virginia Commonwealth University, and Indiana University to advance evaluation science and better define outcomes and impact criteria for our programs. The findings of this group have been presented at national meetings (October 2014, American Evaluation Conference). In addition, our evaluation team, along with a group of 4 other CTSAs and a member of the CDC, formed the Translational Research Evaluation (TRE) TIG within the American Evaluation Association. Our evaluator serves on the governance committee and will serve as the connection to this organizing group. The over-arching goal of the TRE TIG is to explore current, state-of-the-art evaluation approaches and applications, foster communication among evaluators and provide opportunities to discuss existing and emerging techniques to evaluate translational research. It is hoped that this TIG, and the community of practice that it fosters, will help members identify and disseminate successful strategies to overcome challenges associated with translational research evaluation. We will continue to collaborate with these and other CTSA hubs to further improve the evaluation processes suitable for determining the outcome and impact of the programs that our CTSA hubs and related national networks offer. We are also determined to participate in national networks focusing on evaluation and tracking as the opportunities arise to avoid duplicative efforts and learn from the experiences of other CTSAs. Furthermore, in the last five years we have utilized periodic survey tools to better understand the performance of our services and quality of our support programs. We have benefitted from this approach and will continue to use it to obtain feedback from our stakeholders.

2. CTSA hubs commitment to local innovation in processes and methods and in national CTSA network. Improving research processes and methods are crucial for an efficient and high quality research enterprise such as a CTSA hub. We describe our CTSA hub as a **"learning CTSA hub**," learning from collective experience, evaluation tools and processes as well as continuous commitment to quality improvement through local and national collaboration

Efficiency and quality of translational research is not only influenced by the internal CTSA hub operation, but also is affected by the respective external institutional administrative structures. Therefore quality and efficiency needs to be addressed at both spheres taking advantage of our Lean and evaluation programs. Clinical and translational research continues to face increasing regulatory burdens, complex administrative processes and reporting, contracting, price setting and its associated encumbrances, which become intensified when applied to a multi-institutional operation such as ours and will become even more exaggerated when applied to a regional or national network of CTSAs. Based on our "One City One IRB" and our Wisconsin "IRB Master Reliance Agreement," experiences, we regard these encumbrances as surmountable given the right approach and involving the right people, including key administrative personnel who are paramount in creating operational readiness to support the CTSA hub and facilitate its goals. For this reason, we will include the appropriate administrators in the planned CTSI Council in each of our partner institutions. The goals of CTSI councils (described in administration component) include fostering collaboration, complementation and synergy between institutional centers/ programs and CTSA hub. We are committed to improving processes and methods through innovation and adoption of what is tried with success by other CTSAs. As described in this and following sections, we have laid the foundation of inter-CTSA collaboration in the Midwest and beyond in the past five years and are well positioned and committed to expand these collaborations to other regional and national networks to conduct and participate in large scale studies of important clinical questions that may be funded by NIH Institutes/Centers or other sponsors such as industry.

II. Track Record in Translational and Clinical Research

Our CTSA has been positively impacted by a number of strategic institutional decisions and development of new facilities and programs by our Hub partners over the past five years. Space limits us to cite only a few below along with the achievements of our CTSA, its investigators and its trainees presented in insert boxes. Our CTSA has contributed significantly to development of translational workforce, enhancing local, regional and national collaborations as well as integrating resources and intellectual assets of our eight disparate partner institutions, creating a borderless biomedical/translational research enterprise in southeast Wisconsin

TABLE 3. Examples of Institutional Achievements Since 2010	Examples of CTSA Achievements Since 2010
• Development of UWM's Innovation Park on the grounds of Milwaukee Regional Medical Center (where MCW, FH, CHW and BRI are located) bringing UWM faculty physically closer to our CTSA; facility provides collaborative spaces for convergence of research disciplines • Development of CTSA-inspired joint MCW-MU multi-institutional Bioengineering Department (in final stages) • Inauguration of UWM School of Public Health; Inauguration of Dean Dr. Magda Peck, who enthusiastically supports CTSI	• 93 CTSA scholars graduated from our combined Translational training and educational programs; published 471 manuscripts reporting their research findings, filed 3 patents and collectively obtained over $12 million in extramural funding • Catalyzed formation of an average of 17 multi-disciplinary teams/yr • Supported 388 new active protocols among a total of 846 active protocols with over 20,000 subjects visiting our three TRUs resulting in nearly 750 publications. • Developed a dedicated Biomedical Informatics Team that successfully operationalized our Clinical Data Warehouse, which currently includes over 1.3 million lives; the addition of CHW's pediatric EPIC data will be complete by March 2015. Our biomedical informatics capabilities enabled our participation in the Greater Plains Consortium
• Acquired and operationalized a 7-Tesla magnet, a powerful tool for translational and clinical research (2013) • MCW investigators for the first time used genetic sequencing (whole exome) to diagnose and successfully treat an unknown disease (2010) • Developed a new bioinformatics software tool designed to more easily identify genetic mutations responsible for cancers. (2013) (Yan Lu, Ph.D., and Pengyuan Liu, Ph.D., both Physiology, and Xing Hua, Ph.D., National Cancer Institute) • Invented novel epoxyeicosatrienoic acid (EET) analogs and soluble epoxide hydrolase inhibitors (SEHI) with therapeutic value for the treatment of inflammation and of cardiovascular, renal and other diseases. (John Imig, PhD, and William Campbell, PhD, Pharmacology & Toxicology, Camille Falck, PhD, UT Southwestern) (2010)	• Developed and operationalized a Clinical Trial Office with plans to extend its services to all CTSA Partners. • Six CTSI-supported investigators are patent applicants at end-stage of commercialization nearing FDA approval (see examples)below) • Collaborated with OCCRIC a joint MCW and FH system operation committee for use of hospital resources for research and made the following improvements: Reduced application-decision time, services used for research provided at cost. • MARCH: Founding member of Midwest Area Research Consortium for Health • Region and State IRB facilitation (One City One IRB, Master Reliance) • Enhanced academic value for Translational research and Team Science: • Annual Dean's Award for Clinical & Translational Research (MCW) T. Michael Bolger Award for Translational Sciences (Regional) MCW Dean/UWM Chancellor App Challenge for Innovative App development supporting translational science/research (multi- institutional)

Regional RIPCI. The Regional Intellectual Property and Commercialization Initiative is an example of practical collaboration in a shared environment among our partner institutions which is transferrable to inter-CTSA collaboration. The Regional RIPCI was developed in year three of the last funding period in response to a recognized need for a collaborative approach to this topic. A multi-institutional study followed. Among several issues identified is that commercialization of inventions can have tremendous value as a highway to patients

and clinical practice, but most scientists and physicians do not always have the knowledge needed to move the idea from original discovery through the licensing and commercialization process. To help remedy this shortcoming, RIPCI developed a series of web-based video learning modules (available through our website) designed to introduce researchers to the technology transfer process. These modules have been offered for use to the technology transfer offices across the universities in the US and elsewhere via the Association of University Technology Managers (AUTM) directors through their communications network. These efforts have the potential to be elevated to an inter-CTSA collaborative project in the next five years commensurate to NCATS programmatic agenda.

Regional DDRI. The formation in year four of Our “Regional Drug Discovery and Repurposing Initiative” is another example of our regional collaboration to advance translation. The Regional DDRI has brought together leading drug and device development experts, regional ANGEL investors, non-profit business development organizations in SE Wisconsin and our partner institutions intellectual property commercialization officers, who are sharing their expertise in the various steps of drug discovery and device development up to clinical development of next generation medical products in a collaborative environment. The Regional DDRI has been successful in forging public/private partnerships and so far has secured one matching grant from the State of Wisconsin Development Office to support early stage studies in the commercialization process. We have advanced this program as an optional module with RIPCI to assist our investigators in bringing their discoveries to product and beyond. We have invited the Concordia University School of Pharmacy to join our CTSA hub as a collaborator (see letter of support). Dr. Dan Sem, a Concordia School of Pharmacy faculty with substantial experience in this field has joined our team to lead this module. The School of Pharmacy has opened an extensive laboratory facility in the innovation center at the Milwaukee Regional Medical Center ground, which also houses investigators from UWM and as planned from MCW and Marquette University adding to our borderless research environment.

One city one IRB and Master Reliance Agreement. Through its MCW partner, our CTSA has expanded the number of its Master Reliance Agreement partners to include greater Milwaukee County and southeast Wisconsin, and to operationalize the **One City One IRB process** (currently including 25 hospital systems in southeast Wisconsin) to institutions as far away as University of Wisconsin –Madison CTSA and the Marshfield clinic in the center of the state. **The One City One IRB Consortium** currently is working on two projects: the "Records Project" that seeks to develop consensual procedures for medical record review studies across the multi-county area; and the "Minimal Risk Project" that seeks to develop consensual procedures for any minimal-risk study. This regional collaboration exemplifies a shared mini-environment created to advance research along the translational continuum, which lends itself to inter-CTSA collaborations. These examples are in addition to other components of the shared translational research environments that have served our investigators in the past five years and the proposed modules that constitute various elements of our shared environment in the future as described later in this proposal. Below we present several examples of how the resources of our shared environment have been used by investigators by our partner institutions.

During the past five years, we have collectively worked hard to remove barriers and obstacles to creating our borderless research environment, while creating opportunities for collaboration and synergy among our multi-institutional faculty. These efforts include creating two new faculty tracks for CTSI adjunct faculty for those holding a terminal degree and CTSI Scientist/ senior scientist track for those who do not hold a terminal degree, such as nurses, biomedical engineers etc.). We provided the opportunity for our non-medical faculty from our partner institutions to have access to services and support at MCW and be able to conduct patient related research in our partner hospitals by issuing them a **CTSI Passport** to be able to navigate the health system. Reciprocal appointments on an as needed basis also have been made by our degree granting partners for accessing their research resources. With the increase in translational work force and depth and breadth of translational research in southeast Wisconsin, we envision that the need for access to resources of our partner institutions will increase and hence the need for these joint appointments. We have developed a comprehensive list of our core facilities available in each partner institution and created instructions on how to access them. This information is easily accessible on our website.

Our translational research units(TRU) fully supported by our institutional braided funds have been made available to faculty of all partner institutions for the past five years and on average, support over 140 projects each year. Similarly our educational and training programs have been borderless for students and scholars

from diverse background and home institution been taught by faculty from our partner institutions further contributing to the development and enrichment of our shared environment. As seen in each module in this proposal, our services and supports provided by expert faculty from our partner institutions follows the principal of complementation and synergy as well as consideration of enhanced needs for services.

B. Our system-wide approach to how patients receiving care at our hub will be made aware of ongoing research and are invited to partake in research opportunities.
Integration of research and clinical care is necessary for advancing translational research. Every patient care encounter should be considered a potential research encounter and an opportunity to either formulate a hypothesis for solving a clinical problem, improve diagnosis and treatment, or recruit new research participants. Patients and representative communities of appropriate stakeholders should be involved in the development phases to help identify research needs and determine whether the outcome of the project will realistically help improve patient care. These ideas are incorporated into our funding mechanisms and processes for reviewing and awarding pilot grants reflecting an acculturation that demonstrates the importance of research and the need for its facilitation in a successful learning heath care system. Research is integrated into clinical practice from two aspects, 1) provider related, and 2) patient related. Limitations to the provider involvement are mainly due to time constraints/economic pressures and lack/limited opportunity. On the other hand, limitation imposed to the participation /involvement of patients in research includes both the effect of provider limitations as well as un-readiness of health care enterprise for this endeavor. These shortcomings have been addressed in our hub, and we intend to take the necessary steps over the next five years to address these issues, such as: a) initiating a Hospital President's award to support clinical and translational research given annually to an operational unit for their significant contribution to conducting translational research, b) offering tailored research support training for clinical staff aimed at reinforcing participation in a learning health care delivery system which improves by adopting research findings that leads to best practices and reinforce the institutional cultural value of clinical research and the importance of finding ways for being helpful to the research process without negatively impacting the clinical efficiency, c) creating a non-monitory incentive for clinical staff facilitating research in clinic, d) establishing an in-kind contribution of health system to research by allowing selected nursing staff a reasonable amount of time for supporting research in clinics, and e) providing the opportunity to every patient to benefit from and contribute to advancing health through participation in translational research. Such efforts include "opt in or opt out" choices for research use of clinical data and specimens in the consent form for clinical care in our partner health systems, and routinely informing adult patients and parents of children coming for care to our CTSA hub health systems of the ongoing clinical trials and research projects that may be available to them, using innovative none intrusive, HIPPA compliant communication tools with option for enrollment. We have beta tested the use of the "My Chart" module of EPIC successfully to provide an avenue for patients to access ongoing research opportunities, research education and potential participation.

IV. Workforce Diversity, implementation of a Clinical and Translational Science (CTS) Portal. We are committed to enhancing workforce diversity, and have adopted a number of approaches to achieve this goal. More notably we recognize the importance of a viable pipeline from high school and undergraduate programs to our graduate and post-graduate programs. These efforts are discussed in detail in our KL2 and TL1 modules. The CTS work force Diversity Portal briefly presented here is designed to increase the participation of underrepresented (UR) students and faculty in biomedical research enterprise. The CTS Portal focuses on cultivating the educational spectrum - from high school juniors to college undergraduates to medical students to physician scientists or similar tracks to other biomedical sciences. It creates a deliberate linkage between our CTSA hub partner institutions and individuals interested in biomedical research at all levels and is designed to assist them in transitioning between the levels of their educational preparation. This Portal will target gender, ethnicity and those from disadvantaged backgrounds and is aimed at educating, training and retaining biomedical, research scientists and leaders.

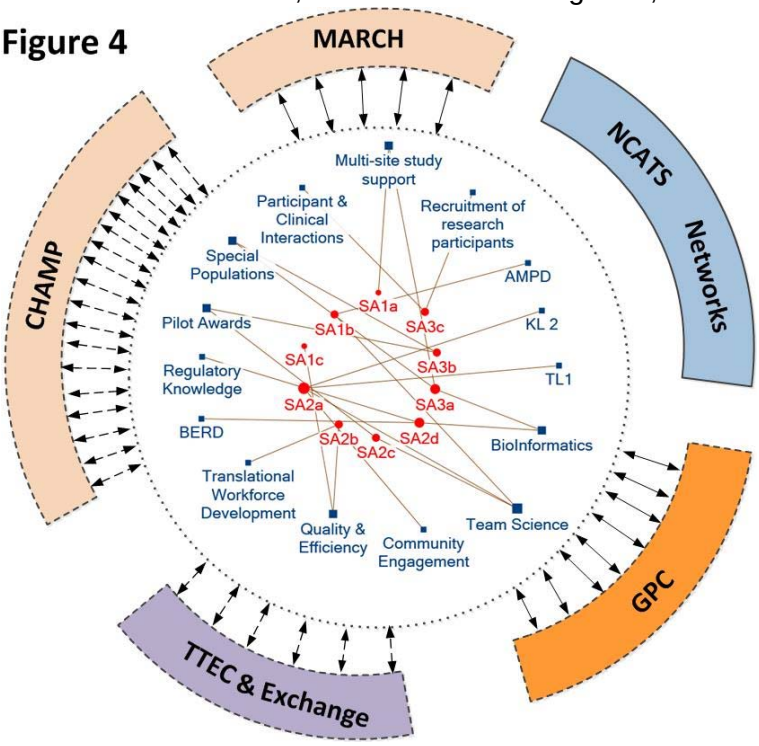
Specifically the CTS Diversity Portal will **1)** develop an academic enrichment and exposure program for UR and disadvantaged high school juniors and seniors to increase awareness of biomedical research and associated career opportunities, **2)** develop an academically-rigorous undergraduate program to provide academic readiness and clinical and biomedical exposure to UR students in the pipeline, 3) develop strong academic skills in medical and biomedical education and provide opportunities for continued biomedical research, and **4)** recruit and retain UR faculty through strong mentoring and incentives to participate in biomedical research.

In addition, each of the participating organizations is committed to enhancing diversity among its employees, faculty, students, and in health care organizations, in its patient population. For example, the 2014 Froedtert Health Community Benefit Report noted the pledge of $2 million to help with an expansion of the Lisbon Avenue Health Center, a federally qualified health center in the area. It also won the North Central Minority Supplier Development Council for its commitment to economic development of minority-owned business enterprises in local communities. In March 2014, Froedtert and the Medical College hosted Health Care 101 Career Fair for high school students; 160 students and their guardians met with staff. For ten years, Froedtert Health has provided scholarships to minority students who are studying health-related degrees at UWM; there is also a scholarship [program for underrepresented student in 13 health sciences programs at Milwaukee Area Technical College. These efforts, made by just one set of CTSI members, are illustrative of the many efforts by CTSI members currently underway to make connections with local underserved communities. The name recognition, education and loyalties engendered by effort of this type will continue and be enhanced, so that the CTSI hub can attract more diversity in all of its activities.

EPILOGUE

In the preceding pages, we shared a high level view of our current and proposed CTSA hub and highlighted its arresting features. We described the components and modules that constitute our translational engine whose direction was delineated in our overall specific aims. We also elaborated about the workforce that will guide this engine to its destination of improving health through research and discovery. We shared our view that the translational workforce, in addition to investigators, must incorporate the appropriate stakeholders and the mechanisms to achieve it. We described how we have linked and operationalized various components/modules of our regional translational engine and how we plan to create a mutually learning Heath Enterprise-CTSA- Eco- System. We described our plan for strengthening our translational science base, how to apply research expertise and methods, how to implement research effectively, and more important, focused on elements of network building and multisite studies. We described our Biomedical Informatics Connectome (BIC) that provides unprecedented connectivity among our Clinical Research Data Warehouse, Faculty Collaboration Database community of stakeholders, Clinical Trials Office, other CTSAs and our hub's services and resources. We showed how our navigator network parallels and complements this Connectome in providing services to investigators, participants, trainees and stakeholders. We have solved seemingly insurmountable challenges and bridged difficult barriers related to IRB and contracting issues. Through trial and error, we have gained experience in how to collaborate effectively, and we are now ready to join the national family of translational networks. In each component and module presented in the following pages, we will discuss what we have learned, what we have accomplished, what we plan to do in the next five years, and how we will do it. We complete this overview with figure 4 to demonstrate how the proposed modules map onto our overall specific aims (center of the diagram) and illustrate the existing (solid arrows), proposed (broken arrows) and anticipated future network collaborations. The number of arrows corresponds to the number of CTSA hubs involved.

Figure 4



MARCH: Midwest Area Research Consortium for Health; a multi-site clinical trials collaboration of five CTSAs
CHAMP: Child Health Research through Multisite Planning; multi-site collaboration of 19 CTSAs
TTEC: Translational Training/Education Collaboratory; educational exchange between five CTSAs
Exchange: Educational collaboration with Harvard Catalyst
GPC: Greater Plains Consortium
NCATS Networks: Proposed national translational science networks

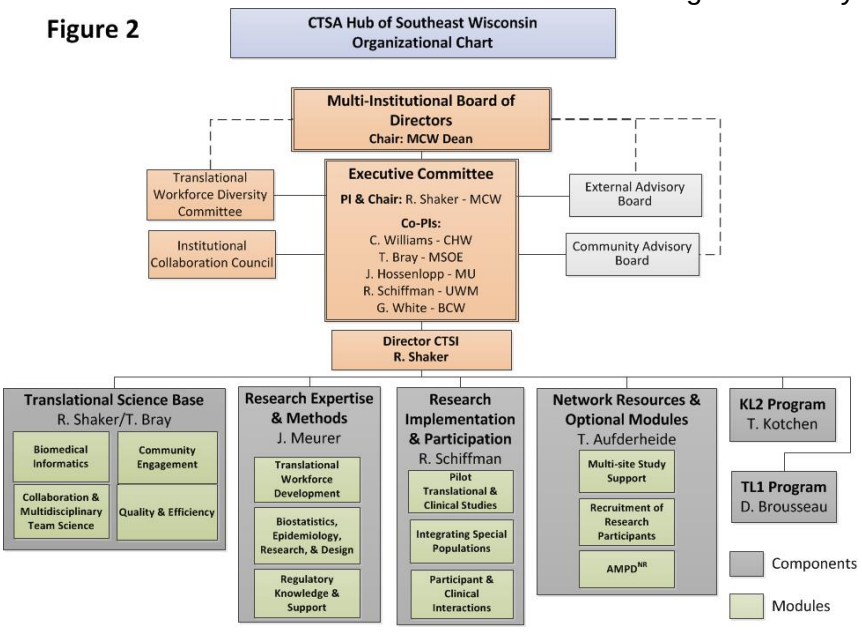
COMPONENT 2. ADMINISTRATIVE CORE **LEAD: R. SHAKER, MD**

A. SPECIFIC AIMS The development of this award proposal for the Southeast Wisconsin Clinical and Translational Science Institute represents a unique and transformative phase in the evolution of the academic institutions and health systems in southeast Wisconsin. We have chosen to build on the rich tradition of multi-institutional collaboration in clinical/translational research, education and training that has flourished in the region through the implementation of our CTSA's (CTSA 1.0) goals in the past five years by continuing our strong regional partnerships involving all of the major academic institutions in the area as active partners in this proposal. We are now ready to play a major role under the current proposal CTSA 2.0 in regional and national network and multi-site studies in accordance with NCATS plans and IOM recommendations. Our CTSA hub partners have executed a legally binding agreement recognizing and supporting the organizational commitments of the multi-institutional body, as described in the FOA. This agreement clarifies the authority of the CTSI itself and validates the creation of the CTSI Board of Directors and the Executive Committee to govern its operations.

Figure 1. Guiding Principles of Governance and Administration of Southeast Wisconsin CTSA Hub/CTSI
Collaboration-Leveraging institutional strengths and resources to enhance trans-disciplinary research and participation in national networks
Transformation-Creating a culture that fosters interdisciplinary innovation and team science
Facilitation-Providing core resources to assist investigators in the development, implementation, analysis and dissemination of CT research findings
Education-Training investigators and research staff in team science, engaging community in their research

The CTSI has created new processes at all the partnering institutions to allow for a borderless multidisciplinary research and educational environment. For example, the MCW Bylaws were changed to permit the creation of new classes of research investigators, such as the CTSI Adjunct Faculty along with a new review process for the MCW Rank & Tenure Committee to confer appropriate designations of rank upon our inter-institutional CTSI colleagues based on their contributions and experience. Now all levels of contributors, both those with and without terminal degrees, will be able to advance the aims of CTSI research moving seamlessly across institutions. We have invited the Concordia University School of Pharmacy to join our CTSA hub as a collaborator to complement our existing investigative expertise and resources and to provide the opportunity to the school of pharmacy faculty to join our translational engine. The Overview outlined our plans; this section describes how our CTSA hub is managed and governed.

Figure 2



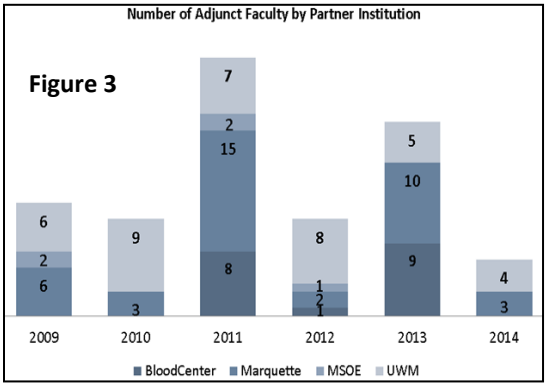
The proposed CTSA uses a participatory management superstructure to organize, align and bridge southeast Wisconsin's academic, clinical and community resources on a common platform, under a unified leadership. The partnering institutions have been integrated laterally and vertically in the CTSA hub to develop a "distinct shared and borderless home" for clinical and translational science; the Clinical and Translational Science Institute of Southeast Wisconsin. We believe our governance and administrative structure is unique compared to individual academic institutions, and given the multi-institutional nature of our CTSI, is well suited to continue to drive the necessary changes, to bridge barriers across institutions and to continue to transform our collective research environment. The underlying principles of our governance and administration are shown in Figure 1.

Figure 2 presents the CTSA hub/CTSI leadership structure which represents our regional partnership at all levels of governance. As a multi-institutional academic entity, this "hybrid" Institute is recognized by all member institutions and thereby, is given the responsibility and authority to offer graduate degrees in clinical

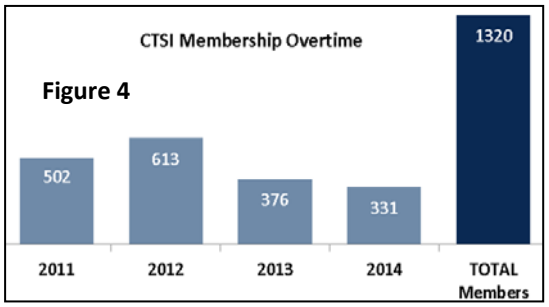
and translational sciences and granting trans-institutional adjunct and secondary faculty appointments to its members. This novel mechanism creates a distinguishing identity for faculty working in translational sciences, while also removing administrative encumbrances to collaboration and access to resources. It also provides an expedient avenue for exercising the CTSI-shared responsibility of allocating resources, protecting faculty research time, and providing salary support and opportunities for promotion. These benefits further serve to foster the creation of a distinctive community of scholars and clinical and translational scientists working together to advance the translational research agenda of our institutions and the NCATS.

PROGRESS REPORT:

CTSI faculty: To date 111 cross-institutional CTSI appointments have been made (figure 3).This is in addition to the MCW faculty investigators. CTSI's membership has also grown precipitously over the past five years (figure 4) and includes not only the investigators, but also the community of stakeholders. In 2013, 21% of investigators benefiting from CTSI services were from partner institutions. This is maintained in 2014 (20%).



Nucleating grant awards: The Administration Core worked with our Pilot and Collaborative Clinical and Translational Program in awarding 87 multidisciplinary proposals in the last five years totaling over $3,770,000 of which $625,000 was from NIH and the rest from our institutional funds. At minimum, faculty from at least two institutions and two different disciplines collaborated in each proposal.



Maturation of our multi-institutional administration: The CTSI EC has continued to meet weekly or bi-weekly during the past five years. We have sharpened our skills necessary to operate a multi-institutional entity. We have in this proposal modified our administrative structure to 1) support fulfilling the goals of this current proposal according to NCAT`s FOA and 2) reflect modifications necessary to more deeply infuse our CTSA goals into the administrative, academic and cultural fabric of our partner institutions.

Budget management: We have managed the NIH and partner institutions' contributions of direct ($1.1) institutional dollars to each direct $1.00 NIH dollar) and in-kind resources to the CTSI for the past five years. Our partners continue to support the CTSI directly (table) and in-kind. This budgetary support has empowered us to: 1) create a biomedical informatics core with twelve expert members fully collaborating and leveraging the bioinformatics capabilities of our academic and health system partners to support the needs of our investigators and create the Southeast Wisconsin Biomedical Informatics Connectome (BIC); 2) develop and operationalize our Clinical Research Data Warehouse (CRDW), which currently includes over 1.3 million lives. The CRDW allows us to actively participate in regional and national initiatives, such as the Midwest Area Consortium for Health, the Greater Plains Consortium and PICORnet (see Biomedical Informatics module for more detail); and 3) develop and operationalize our regional Clinical Trial Office, which will be vital to NCATS' plan for creating CTSA-Support Centers (CT-SC) and CTSA Network Recruitment Centers (CT-RC).

THE CONTRIBUTIONS, INTEGRATED RESOURCES AND EXPERTISE OF CTSI PARTNERING INSTITUTIONS

Our partner institutions collectively complete the continuum of translational sciences by bringing together the complimentary expertise, resources and financial contributions needed to achieve the goals of this proposal. Together, through combined effort, action and investment, each partner institution contributes to the success of clinical and translational research in the region. The total allowable NIH budget of $4 million per year for the CTSA is significant, but it is not adequate to complete the CTSI's overall mission. The additional direct support from our partners is necessary to achieve our proposed goals.

Goal 1. Developing and managing our matrix budget. We have developed a matrix budget that clearly identifies the various resources that are at our hub's disposal. This forms the financial foundation for our strategic planning. Our collective institutions will contribute $3,135,000 annually in direct (Table 1) and over $1.5 million in-kind support (faculty time) to CTSI over the 5 year period of the grant. Furthermore our CTSI goals and services will be supported by the positive environmental impact of complementary resources and services (Overall Section-institutional achievements).

TABLE 1. CTSA and Institutional Annual Support

Partner Institutions	Direct Financial Contributions ($)	Space Contribution (Sq. ft.)	Discipline/Expertise Contributed
BRI	15,000.00	--	Hematology Research
CHW/CRI	700,000.00	2,780	All Pediatrics Disciplines and Research, Special Population
FLMH	1,000,000.00	8,093	Patient-related services, Adult patients, and overall Health System
MCW	1,520,000.00	9,000	Life sciences, Biomedical research infrastructure, All Adult medicine disciplines, Medical school
MSOE	--	--	Engineering technologies, software and hardware, Quality and Efficiency
MU	--	7,000	Health sciences (Nursing, PT/OT, etc.) Dentistry, Computer Science and Engineering, Humanities
UWM	--	--	Nursing, Biomedical Engineering and Bioinformatics, Humanities
VAMC	--	1,000	Patient-related services, Special populations (Veteran & Geriatric)
Concordia U (Collaborator)	--	--	Pharmaceutical Sciences
TOTAL	3,235,000.00	27,873	

Table 2 presents our cumulative resources by component. Support from the CTSA grant (direct cost) is identified as "CTSA Direct," and direct monitory institutional supports are labeled (Institution Direct) respectively.

TABLE 2: Five-Year Component/ Module Support

Component	CTSA (Direct)	Institution (Direct)	TOTAL (Direct)
Admin/Governance	1,011,945	2,962,885	3,974,830
Translational Science Base	4,761,353	2,073,456	6,834,809
Research Expertise and Methods	2,960,125	1,293,875	4,254,000
Research Implementation and Participation	2,101,685	6,543,444	8,645,129
Network Resources and Optional Module	2,218,500	1,321,340	3,539,940
KL2 Program and Inst. KL2 - equivalent	1,529,835	1,980,000	3,509,835
TOTAL	$14,583,443	$16,175,000	$30,758,443

Anticipated problems and solutions. A matrix budget is more challenging to manage than a direct budget; however, the leadership has a minimum of 15 years of experience in complex budget management.

Goal 2. Manage Space Resources. One of the most effective mechanisms for promoting collaboration and cross-fertilization is arranging physical proximity among laboratories with common or complementary interest and expertise, and we will continue to manage our research space accordingly. As outlined in the RFA, the CTSI controls its own space (28,000 sq. ft. see Dean's letter), which comprises the following: administrative space; adult, pediatric and VA TRUs; community engagement module/core, translational technologies and resources space, and bio medical informatics services core. In addition, we will continue to collaborate with department chairs and center directors to ensure that faculty are placed in research space with colleagues who share similar research interests, always with the goal of integrating clinical and translational research with existing programs. In order for this to occur, we will place our translational investigators into existing space. As noted in the Dean's letter, 25% of all MCW's newly assigned departmental and center research space is earmarked for clinical translational research. This space will be jointly managed by the CTSI with department chairs or center directors. Based on the experience of the past five years, we do not foresee any problem in managing the space or related issues that may arise.

Goal 3. Establish the strategic goals of the CTSA hub.

Set annual goals via a strategic planning process. A strategic planning process is in place to set annual goals. This proposal maps the blueprint of goals and deliverables as they can be visualized at this point, but also recognizes that infrastructure needs and priorities will continue to evolve in a dynamic process. Our partnerships may undergo changes as different components are implemented and barriers are identified. Priorities will be adjusted and deliverables potentially modified to align the large number of constituents with the outcomes of each annual strategic planning process. No significant deviations from scope are anticipated

or proposed here; only alterations in implementation or solutions. If a deviation in scope should occur, we will approach the NIH staff with a written proposal prior to making any changes.

FIGURE 5. Steps in the Strategic Planning Process
1. Review results of evaluation materials
2. Review goals of each Module/Component
3. Poll faculty for needs
4. Appoint EC subcommittee to draft plan

The strategic planning process has several steps as shown in figure 5. The draft phase will take 1 month initiated at the beginning of our 4th quarter. The draft plan then will be presented at a one day planning conference, where breakout groups will discuss and recommend modifications. The revised draft plan will be presented and discussed. Final recommendations will be drafted within 2 weeks of this gathering, with final edits made within the next week. This timeline (first 6 weeks of the fourth quarter) ensures that the strategic plan is approved and in place before the beginning of the ensuing fiscal year. The PI will present the final report to the Board of Directors (BOD), which will then evaluate the strategic plan. Adoption of the strategic plan requires a simple majority by the BOD. If the entire plan does not pass, sections of the strategic plan can be vetoed or tabled to obtain additional information. The approved plan will become the guiding document for the next grant year. If NIH requests additional changes, exceptions will be planned. Proper steps are taken for communication and implementation of the strategic plan.

Assist moving research findings along the continuum of translation. This goal will be achieved through "research portfolio management" by the EC, in collaboration with the TRIAD leaders, AMPD optional module leadership (IP experts and Pilot Grant Module), and through the formation of appropriate subcommittees, which will review the portfolio and determine the necessary courses of action to advance pre-clinical and clinical projects along the translational continuum. In doing so, the EC will strive to assure that resources are appropriately matched with needs and opportunities. For this analysis, the EC will solicit recommendations from the Scientific Advisory Board and Component Directors/Leads. The Component/Module Directors' meeting is slated for 1.5 hours every month and will occur as part of the EC meetings, with Component/ Module leaders joining in. The research portfolio will be one of the agenda items, an arrangement that integrates the Component/Module leaders into the portfolio management procedure. This brings a tremendous amount of experience and knowledge to the decision making process, with the understanding that the Executive Committee will make the final decisions.

Anticipated problems. None. The leadership team has extensive experience in strategic planning.

Goal 4. Coordinate and integrate the various components/Modules of the CTSA.

In order to build and enhance our research community, it is essential to provide a variety of forums for interaction and exchanges of ideas, while not burdening the investigator with yet another series of meetings. Figure 6 describes the Administrative Core's coordination role for CTSI-wide activities.

Figure 6. Administrative Core Coordination Activities
1. Develop meeting schedule and coordinate participation of partner institutions.
2. Organize Component/ Module leaders meeting, the annual retreat, EAB, SAB meetings, and faculty and staff events.
3. Maintain the CTSI portal in collaboration with the Bio-informatics module
4. Provide a quarterly newsletter (preferred by many to websites).

The PI and Co-PIs will ensure that Components and Modules operate efficiently as intended, in order to achieve the overall missions of managing the CTSA and directly supporting the clinical/translational investigator. The primary management tools for the overall program will include bi-weekly and monthly meetings (with conference call- in for those who are out of town) to update and discuss the overall operations across the different components of the CTSA. The meetings will be held at MCW in conjunction with the Executive Committee meeting to facilitate the combined participation of the Executive Committee members and the Component/ Module leaders. The first 30 minutes of their agendas will include reports from one or two components. The second 30 minutes will allow discussions related to the cross component functions and inter-CTSI activities, and the third 30 minutes will focus on CTSI research portfolio management.

FIGURE 7. Responsibilities of the Executive Committee, PI and Co-PIs
1. Integrating the cross Component activities and ensuring the quality of the overall program
2.Overseeing governance, setting policy, procedures, structure, AND insuring that all of the Components and Modules communicate with each other
3. Ensuring the Component/Module directors have the budget and resources needed to enable them attain their goals
4. Developing and implementing strategies to improve the overall operation of the CTSA
5. Overseeing the budget, space, facilities, and overall "portfolio" of projects
The Roles of the Component Directors
1. Meeting their goals and adjusting priorities to ensure the PIs (clients) are fully supported
2. Managing daily activities of their modules
3. Participating in the strategic planning process
4. Participating in trans-CTSA and NCATS initiated activities

The roles and responsibilities of the Executive Committee, PI, co-PIs and Component Directors are described in Figure 7.

Component/ Module Interaction. Although all Components report to the PI and the Executive Committee, sharing a strong functional relationship among the Components and Modules is essential to their/the overall CTSI's success. This functionality is actualized through the collaborative forum of the Component/ Module directors meetings, and through inter-service relationships that can be initiated by any Module needing assistance or seeking collaboration with another module. An example is the joint efforts of the Pilot grant and Education/workforce Modules to assist translational degree students apply for research funding.

Anticipated problems and solutions. The current CTSI/CTSA hub activity level depends on connectivity and a solid platform for shared communication in order to operate smoothly. Fortunately, the Administrative staff, assisted by the Bioinformatics group is already coordinating an excellent calendar of events (published on the CTSI website). Our CTSI is fortunate to have assembled a diverse group of leaders well-equipped not only with the skills needed to develop grants, but also to manage and implement processes and programs. Should any of these individuals decide to move on, a sufficient pool of well-qualified mid-career faculty members are available to be groomed to fill any potential leadership vacancies.

Goal 5. Collect Component/Module reports and prepare overall program reports. The Administrative Core, which has gained extensive experience in collecting and assembling materials during the last five years, will be responsible for collecting all reports. We will use our Waypoint (see evaluation) to track activity and to facilitate report generation and to exchange reports and other "paper" materials. This will include assessments of overall performance in conjunction with the evaluation personnel, annual progress reports for the NIH and all documentation for the Scientific Advisory Board and annual External Advisory Committee reviews.

Anticipated problems and solutions. The reporting process itself is not inherently difficult. The major challenge is to convince busy individuals that tracking activities are essential, particularly in an ever increasing "cost accounting" structure of an academic medical center. The primary goal for this aim is to minimize the reporting structure and to maximize the use of the reports generated though Waypoint.
Our Waypoint will be tremendously helpful.

Goal 6: Develop and Implement Governance Policies. Appropriate multilevel governance and management mechanisms within the purview of the CTSI have been successfully implemented to facilitate cross institutional integration (see figure 1). The CTSI is structured as a multi-institutional academic entity. This novel mechanism creates a unique, distinguishing identity for faculty working in translational sciences, while also removing administrative encumbrances to collaboration and access to resources. The CTSI-shared responsibility of allocating resources, protecting faculty research time and opportunities for promotion further serve to foster the creation of a distinctive community of scholars and clinical and translational scientists. Our governance strategy is outlined below:

Oversight. Two different boards are responsible for the oversight of our CTSI:
1. The Board of Directors (BOD) is comprised of the highest ranking academic or administrative authority of the partnering institutions: Dr. Joseph Kerschner, Dean of the MCW Medical School, who serves as the Board's Chair, Dr. Johannes Britz , Provost of UWM, Dr. Margaret Callahan , Academic Provost of MU, Dr. Fred Berry, Academic Vice President of MSOE, Jacquelyn Fredrick, President and CEO of the Blood Center of

Wisconsin, Ms. Cathy Buck, RN and Ms. Peggy Troy, RN the CEOs of Froedtert and Children's Hospitals, respectively, and Dr. Michael Erdmann, Chief of Staff of ZVAMC. The Board of Directors provides the framework conferring the authority needed by the CTSA leadership across institutions, creates a unified, strategically aligned mechanism to direct the enterprise and promote complementation and collaboration, overcomes potential administrative and legal barriers, and oversees the CTSA's progress. The PI of the CTSA hub/CTSI reports to the Board and its Chair. The role of the Board of Directors is equivalent to that of a public company (figure 8).

FIGURE 8. Responsibilities of the Board of Directors

- **Meets quarterly to review progress; each Board member has an a-priori approved designee to attend if needed; however, this substitution has occurred rarely in the past five years due to the strong commitment of the leaders.**
- **Approve all governance policies;**
- **Participate in the selection of the PI through recommendations and advice to the Dean of MCW;**
- **Approve all co-PIs and Component Directors;**
- **Evaluate and replace CTSI Director (CTSA-PI) and co-Directors as needed;**
- **Approve the annual Strategic Plan;**
- **Provide a forum for the leadership of the partnering institutions to assess scientific infrastructure needs and opportunities between them. These quarterly meetings have helped align the investments in research infrastructure between the institutions; minimizing duplication and leveraging strengths between them. Representative examples include our CTSA-inspired planned multi-institutional Engineering Department (MCW, MU) and an undergrad Under Represented pipeline between MU and MCW.**
- **Oversee the alignment of the CTSI's and the partnering institutions` research agendas and growth plans.**

The CTSI Director and Co-PIs will undergo a "360" Critical Review every two years by a panel chaired by a senior member of MCW or its partner institutions not involved in CTSI management, who can provide feedback from a broad base of the CTSI community. The review will be shared with the CTSI Board of Directors and External Advisory Committee. The Dean of MCW, on behalf of the Board of Directors in collaboration with the External Advisory Committee, will provide feedback to the Director about his or her performance, the areas in need of improvement or change, as well as any other concern specific or general about CTSI management. Each Co-PI will undergo a similar review and the results will be shared with the CTSI Director who will then provide feedback in consultation with the BODs to Co-PIs. In the case of significant underperformance, the Dean in consultation with the above governing body will have the authority to replace the PI. If for any unforeseen reason Dr. Shaker becomes unable to perform his duties as the PI of this application, Dr. Calvin Williams will serve as interim PI until a new PI is appointed by the Dean of MCW in consultation with NIH.

BOD Member Requirements: Members must be senior leaders, preferably Deans for the academic partners, or the CEO of the hospital and business partners. Another senior leader may be appointed, but this individual must have the ability to make decisions for the institution with respect to the CTSA. The NIH program officer will be an observer member of this committee (non-voting member).
Appointment process: Members of this committee will be appointed by the respective partner institutions. Each institution will appoint one member. Term: No maximum.

2. The External Advisory Board. The BOD oversees the CTSI, but it is composed of leaders from all CTSI partners, and thus it is not unbiased. Furthermore, the BOD is not comprised of many clinical scientists. The External Advisory Board (EAB) (mandated by the NIH) has served us well in this capacity for the past 5 years, and we have benefitted from its advice. This group has been introduced to NCATS in our letter of intent. Their recommended roles continue to be 1) reviewing the grant and each subsequent strategic plan, and 2) annually reviewing the overall program as required in the FOA.
Member Requirements: Each member will continue to be a PI, co-PI or Module/ Component Director of another CTSA hub or other NIH required expertise. The expertise of the 3 external members will be complimentary and with minimal overlap to provide the broadest coverage of our CTSA (see evaluation).
Appointment process: The PI in consultation with co-PIs will make recommendations to the Board of Directors, which will then select from nominated candidates. Term: 36 months, staggered start dates to have at least 1 member who has been through the previous review.

Operational Oversight. The Executive Committee is responsible for operational oversight of our CTSA hub.
3. Executive Committee. The Executive Committee (EC), chaired by the PI and comprised of the PI and co-PIs representing each of the partnering institutions, have worked together closely to oversee the transformative process for achieving our CTSA hub`s goals in the past five years. The EC has helped to reorganize and realign resources, designate institutional leadership, maintain connectivity through this committee and provide

direction in the overall management of the CTSA. The Administrator of the CTSI (a non-voting member) is responsible for preparing and presenting to the EC a comprehensive quarterly report reflecting the milestones established by the Evaluation and Tracking metrics, resource utilization and measures of quality, and the productivity of each Component/Module of the CTSI. This process will permit the EC to assess and address issues regarding under-, over- or inappropriate use of resources, productivity or other problems, and to adjust plans or reallocate resources, if necessary.

4. Institutional CTSI Collaboration Council (to be implemented in 2015). The CTSI Collaboration Council, comprised of research leaders in each partner institution (Research Center Directors and research deans), is the mechanism connecting CTSI to the centers and programs of excellence that are unique to each partner institution. This mechanism helps to foster complementation and synergy, align goals and research agendas, and avoid unnecessary duplication, and we anticipate it will further our collective translational goals faster and more cost effectively.
Member Requirements: Members will be Institute, Center or Program Directors or administrative units in the partner institutions, including our health systems, which have complementary charters or provide services crucial to translational research and CTSI.
Appointment process: Members will be appointed by the institutional leaders who are members of the BOD in collaboration with the PI and EC. The PI and co-PIs (EC members) of the CTSA will chair these councils in their respective institutions. Term: Five year renewable.
Anticipated problems and solutions. We do not anticipate any problems with the governance. Thus far, the oversight (Board of Directors) and management (Executive Committee) committees, as well as the functional units, have operated very well. Only small modifications have been made over the years or are anticipated in the future. The current structure is working effectively, as evidenced by the substantial progress we have made in the past five years toward implementing the goals of our CTSA1.0 (see Overall).

5. Community Advisory Board (proposed to be implemented this year). The Community Advisory Board is comprised of representatives of our community of stakeholders, such as local community organizations, patient advocacy groups, patient community, community members at-large, industry and government. Composition of this board will be suggested by the EC in collaboration with the CE module, and approved by the BOD.

6. Translational Workforce Diversity Committee. This committee (see Overall) will advise CTSI Hub on strategies to increase diversity in the translational workforce, including plans for effective follow-up and tracking, such as annual review of diversity status and make recommendations based on annual diversity data.

7. The Component/Module Directors (KFD) Committee, comprised of the Directors/Leads of all Modules and Components of this grant, will meet monthly in person or by electronic means, such as Mega Meeting to discuss overall operations across the different components of the CTSA.

Faculty appointment to CTSI: Request for Adjunct, CTSI Scientist and Secondary appointments to CTSI comes to the PI through the Institutional representative on the EC who will write a letter of support describing the applicant's anticipated contribution to the overall mission of CTSI, such as teaching, research and collaborative potential. The letter also will describe how the faculty likewise will benefit from CTSI membership. The applicant must initiate the process by submitting a letter of request, accompanied by a letter from his or her department chair. The PI will ask the EC to review the materials and make a recommendation. Based on the EC recommendation, the PI will recommend the candidate to the Rank and Tenure Committee (R&T) for consideration of approval. Secondary appointments (only for MCW faculty) do not require approval from R&T committee and will be granted by the PI. All types of appointments will need final approval by the Dean.

Evaluation and Continuous Improvement. The overall evaluation is driven by two overarching questions rooted in CTSI's mission and primary theory of change (figure 9). The primary goal of CTSI evaluation focuses on providing internal and external stakeholders information to guide ongoing program development and

improvement through performance monitoring and process evaluation, and summative information to determine the degree to which intended (and un-intended) outcomes are achieved. A range of approaches are deployed to monitor and evaluate CTSI services and cross-cutting, transformative initiates working towards CTSI's long-term goal. Given the nature and environment in which the CTSI operates and the evaluation questions outlined above, a mixed-methods design using both qualitative and quantitative data sources and analysis techniques will be used (see logic model and data collection plan in the appendix for more details). Qualitative data collection techniques and the rich information they yield provides compelling evidence of the change process, while quantitative techniques and the information they yield provides evidence regarding contribution (cause-effect relationships), enables us to test specific hypotheses, describes the characteristics about our CTSI and examines specific relationships that exist between activities, outputs, and outcomes.

Figure 9. 1. Are we succeeding at what we are doing (transforming the way in which clinical and translational research is conducted in southeastern Wisconsin? (see CTSI mission statement)

a. How successful are we at identifying and minimizing the inefficiencies, barriers, and bottlenecks to conducting clinical translational research?

b. How successful are we at providing innovative solutions and techniques to advance/propel clinical translational research?

2. What is the impact of this investment of resources on the quality, efficiency and cost-effectiveness of clinical and translational research?

a. Do the resources and services we provide lead to high-impact, quality clinical translational research?

b. Are our services delivered in an efficient and cost-effective way?

c. Are our investments leading to more team-based, high-impact clinical translational research?

The evaluation approach utilizes best practices in the field [1]– the CDC framework for program evaluation, the American Evaluation Association (AEA)'s program evaluation standards, and logic models and data collection plans (see appendix) as the roadmaps to communicate the complexity of the CTSI and assist in identifying key metrics for CTSI and key services. CTSI's overall evaluation approach is:

1. Utilization-focused: done for/with specific primary intended users, for specific intended uses [2]
2. Participatory: engaging and involving stakeholders at all stages of the evaluation as stakeholders are those that need data to make decisions and communicate the successes and challenges of their work;
3. Methodologically flexible: utilizing a mixed-method (quantitative & qualitative) approach and triangulation of multiple data sources to answer evaluation questions and;
4. Developmentally focused: the evaluation design and implementation evolves and changes throughout the grant period as the context changes; data from early phases of implementation are used to refine plans and to provide recommendations for improving structures and processes [3].

This evaluation approach is most appropriate for large innovative initiatives operating in dynamic and complex environments where conditions, interventions and participants are unsettled and pathways for achieving desired outcomes and impacts are less certain.

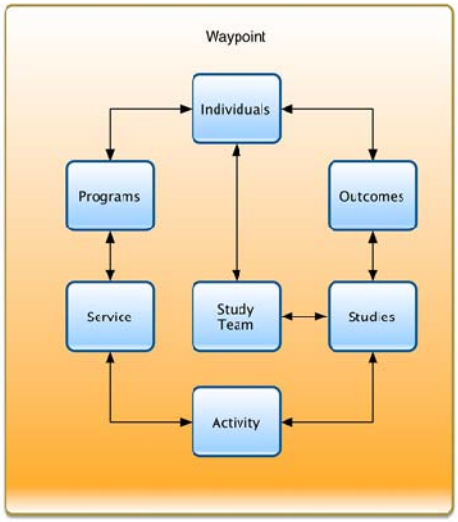
Figure 10: Waypoint© within the CTSI

The CTSI evaluation core is comprised of one full-time internal program evaluator, reporting to CTSI Administration, and a database analyst, reporting to Biomedical Informatics. The two collaborate and work closely to achieve the overall aim of evaluation and continuous improvement. CTSI consolidated the evaluation 'key function' into the Administration core in 2012; a common practice in about 34% of CTSAs (2013 CTSA National Evaluators Survey). The change has resulted in a more comprehensive, integrated and holistic evaluation approach across CTSI. We utilize logic models and data collection plans (see appendix) to help organize and coordinate the systematic collection of metrics across our programs and services. Using data collected overtime, we have appropriately modified some of our programs, services, and initiatives, in fact implementing logic models and data collection plans for each core, allowed for data to be collected in a more systematic way and aggregated at a global CTSI level. However, it was through this approach that we recognized the need for a more central system to track and store data. Therefore, evaluation efforts shifted in 2013 to focus on strengthening the evaluation infrastructure and

systems across all cores and services in order to better assess the use of new or enhanced services and the outcomes of this usage. The ultimate goal is to become a more data-driven enterprise in which service development and refinement and business and strategic decisions are guided by evaluation and business data, and a standardized evaluation process is created across the CTSI enterprise.

Based on our EAB's recommendation in 2012, evaluation and biomedical informatics partnered to design and develop a centralized database, called Waypoint© (figure 10). A centralized system allows us to systematically track the investigators who have benefited from CTSI resources and services in a more real-time fashion, understand where efficiencies can be gained, better assess what has happened as a result of our support (e.g., publications, collaborations, grants, discoveries and technology patents, etc.) and better identify changes taking place across our institutions and communities as a result of our CTSI. Phase 1 of the development was successfully completed in 2013-2014, with full operalization expected in year one of this proposal.

Figure 11: Waypoint© Data Model



In order to maximize existing data in systems across CTSI and MCW, Waypoint© utilizes web services technology to connect to our CTSI website (where membership data, request for service data, and conference registration data are captured) and our TRU database (figure 11). In the next five years, we will pursue connections with our Faculty Collaborative Database (FCD), and other public databases such as NIHExporter/Reporter and PubMed to maximize automation and outcome reporting and minimize human error.
All CTSI enterprise data will be captured or connected with Waypoint©; it serves as the primary method in which process and outcome metrics are captured and collected across CTSI program and services. Formalized and standard metrics outlined by NCATS will be captured, monitored, and reported via Waypoint© (if they are not already) or captured in other database systems that are connected to Waypoint©. We welcome a more formalized evaluation process and standard metrics outlined by NCATS. In 2013, our CTSI was one of 12 other CTSAs to participate in the national Common Metrics Workgroup. The results of this study provided critical lessons learned about the feasibility of collecting and utilizing common metrics at our CTSA and others [4]. We are fully ready and able to participate in the further refinement and eventually reporting on common metrics across CTSAs. Over the years, we have developed close working relationships with entities across our partner intuitions that house data we may not be able to access directly, but are part of the research process (e.g., Office of Research, Grants and Contracts, etc.). These offices were engaged during our national pilot project and are fully ready to collaborate with us and share data, as necessary. Where possible, Waypoint© will connect to existing systems to create a comprehensive picture of research processes, key touch points and roadblocks that might exist (e.g. REDCap™, Clinical Trials database, Grants and Contracts database, IRB database, etc.). Other data collection tools utilized by CTSI for evaluation purposes include REDCap™ and the Graduate Tracking Survey System (GTSS). GTSS is utilized by CTSI's education module and was developed by the Rockefeller Univ. CTSA. GTSS captures individual-level data (e.g., publications, presentations, funding, clinical trial participation, patents and technology transfer products and appointments), on all CTSI education participants utilizing four public databases and request that the respondents validate their products which aids in the validity and reliability of productivity and outcome data (see TL1, KL2 and TWD section for more information).

Leadership will have access to and receive quarterly dashboard reports and annual reports authored by the internal program evaluator. An Evaluation Workgroup will serve as the primary driver of database development, defining key metrics and terms and deadlines for key data collection phases across CTSI. This workgroup, which includes a member from each CTSI core, the CTSI internal evaluator and the database analyst, was created in early 2014 to create a more data-driven evaluation culture and has been an important driver of database development work. LEAN teams will be leveraged to work on short-term process

improvement projects and work in close collaboration with CTSI's internal evaluator to ensure a holistic and comprehensive approach to improving the efficiencies and outcomes CTSI aims to achieve. Milestone goals for our CTSA hub will be monitored annually utilizing the Annual Progress Report. Each module will report on milestone goal achievement and new milestones developed for the coming years via the APR in a collective and systematic way. Summaries of overall progress will be provided to the CTSI leadership by core on an annual basis for appropriate action, decisions, and discussions.

Table 3: Researchers, Publications & Grants Supported by CTSI, by Year

	2010	2011	2012	2013	2014
Researchers Benefiting from CTSI Services *(Biostatistics, PCIR, Education, Pilot, BMI, TTR, Reg, and CTSI workshops and other ancillary administrative services)*	n/a	153	372	764	1081
CTSI Supported Publications *(source: PubMed)*	1	15	80	129	89
Grants Secured by Investigators Benefiting from CTSI Services *Includes: Education (degree programs, KL2s, etc.) and Pilot Awardees ONLY*	11	23	33	26	21

Evaluation data will continue to be summarized annually (or at key intervals, such as cohort completion, EAB visits or when key data are available, etc.), and shared with program staff and CTSI leadership. Findings and the potential need for changes will be shared with the relevant parties in a timely manner. Broadly, findings are disseminated in partnership with CTSI and its modules, the CTSA consortium and the NIH through various channels. Official evaluation reports are provided to CTSI administration for scheduled reporting periods and as available. Various short reports and presentations are drafted and provided as required for CTSI administration and its oversight committees, as opportunities arise. Preliminary evaluation findings are presented to the CTSI leadership team and the External Advisory Board on an annual basis (or as necessary) so that decisions and any necessary action can be taken, such as further evaluation, dissemination of winning strategies, or the sunsetting of strategies failing to meet targets or expectations. In the next five years efforts will focus on publishing more evaluation reports and data via the CTSI website in an effort to make the attainment of key outcomes more transparent and accessible to our range of stakeholders, including community members. The CTSI External Advisory Board (EAB) plays a pivotal role in the overall evaluation of our CTSA. Our EAB is comprised of five members from five different CTSA institutions (see table 4). EAB members have provided great insights into the successful operation of CTSAs. Over the years, our EAB has provided several important recommendations for which we have implemented necessary processes/changes (see table 5 for sampling of examples by year).

Table 4: CTSI EAB Members

Name	CTSA	CTSI EAB Role & Expertise Area	Member Since
Harry Shamoon, M.D.	Albert Einstein, Director of the Institute for Clinical & Translational Research	Chair, General	2009
Lauren S Aaronson, RN, PhD, FAAN	Kansas University Medical Center, Deputy Director	Member, Community Engagement	2013
Michael J. Becich, M.D., PhD	University of Pittsburgh, Associate Director of the CTSI and Chairman of the Department of Biomedical Informatics	Member, Biomedical Informatics	2009
Edward Ellerbeck, M.D., MPH	University of Kansas, Cancer Center Chair and Professor, Department of Internal Medicine	Member, Education and Pilot Award Program	2013
Julie Rainwater, PhD	UC Davis Clinical and Translational Science Center, Director of the CTSC Evaluation program	Member, Evaluation and Education	2013

Table 5: CTSI EAB Recommendations & Resulting Action (sample)

CTSI Area/Core	EAB Recommendations by Year[1]	CTSI Action/Implementation by Year
Biomedical Informatics	1. Lack of focused plan for clinical research data warehouse (2011) 2. Need to figure how to provide support to other partner institutions' investigators and provide them with broad access to clinical data, biospecimens & informatics tools (2011, 2012)	1-2: Implemented i2b2 technologies and connected with hospital EMR system (2012-2013) and plans to access Children's in 2014 (on-going); crated a storefront for access to clinical research data (2013) 3: Matrixed leadership involving Research IT

[1] CTSI had two EAB meetings in 2011 (January and November) and one each year thereafter, except for 2014.

	3. Lack of dedicated leadership for Biomedical Informatics remains a problem (2011) 4. Lack of direction and leadership for Biomedical Informatics at MCW (2011) 5. Consider elevating Brad Taylor, Research IT leader, to Chief Research Informatics Officer (2012)	leader and working groups to recruit Director of BMI (2012) 4: secured PCORI funding and participation in Grater Plains Consortium (2013) 2-5: Created a central 'home' for BMI within CTSI and promoted Brad Taylor to CRIO (2013). Regular consults/services available to all CTSI partner investigators via website and 'concierge service' (2013)
Education/Workforce Development	1. Number of K scholars is very limited (2011) 2. Embrace the MSTP program and encourage inter-mingling between K and MD-PhD students (2011) 3. The innovation of the education program is not entirely clear. For example are there innovative programs in education delivery (web-based JIT, etc.). (2012)	1: Buy-in and cost sharing from institution to fund additional non-NIH K awards, thus increasing the number of scholars at a steady state from 1.5 to 6 scholars (2011-2013) 2: Created a "K-club" where trainees, scholars and MSTP participants engage with each other 3: Changes described within proposal for next five years (2014-2020)
Community Engagement	1. Lack of clarity between roles of Dr. Maurana as co-chair of the Citizens Advisor Committee and Dr. Ahmed as Director of CE (2011) 2. No clear engagement of CBRNs (2011) 3. Lack of evidence that shows collaboration between partners (i.e., evidence of training support for non-MCW institutions) (2012) 4. Lack of evidence that core is working with investigators across translational research spectrum (2013) 5. Risk of becoming a 'siloed' community program (2013)	1: Dr. Syed Ahmed became co-chair to CAC (2012) 2: CBRN moved to PCIR and lead by Dr. Jeff Whittle (2013) 3: Created CBPR training course, open and accessible to other partner institutions (2013) 4-5: Think-thank with basic scientists on what their community engagement needs are (2014) and other changes described within proposal for next five years (2015-2020)
Evaluation	1. Means for collecting data for diverse metrics across key functions and institutions is not clear (2011). 2. Need to show incremental changes via trend analysis on key outputs and outcomes (2012) 3. Inter-institutional collaboration opportunities may be overshadowed by too much focus on MCW; intentional measurement of inter-institutional activity could convert this to an opportunity (2012)	1-2: Instituted 'nested' logic models and data collection plans for CTSI as a whole (Macro level) and key cores (micro level) (2012-2013); developed Waypoint© in collaboration with BMI 3: Analyze and report data through the lens of inter-institutional make-up (service use, applications received, etc.) (2013)
Biostats	1. Need to figure out how to provide support to other partners (MU, UWM, BRI, etc.) (2011) 2. More interaction with Education, PCIR and Biomedical Informatics is encouraged (2011).	1: Drop in services provided at MU, FH, and CC (2012-2013) 2: Biostats faculty serve on thesis committees and as mentors to CRS and KL2 trainees (2012)
Pilot & Collaborative Funding	1. The number and percentage of funded projects could be increased in several ways: decreasing the size of awards, asking for matching funds, or offer very small ($2500) awards (2011) 2. Need to track ROI of program, given large amount of institutional investment in this program (2012) 3. Pilot review process takes a long time (2013)	1: Modified sizing and duration of awards (1 year awards/~$25,000-$50,0000) and secured other funds for pilot awards (AHW/institutional funds) (2012-2013) 2: Instituted systematic quarterly reporting (with collection of key indicators and outcomes) using REDCap™ and planned follow up for completed projects (2012-2013) 3: Revamped review process and aimed to decrease the reviewers time by 4 weeks, but given nature of volunteer reviewer pool, a small percentage of reviewers were unable to meet the deadline. We will continue to work on this in the coming years (2014)
Participant Research Interactions (TRUs)	1. Lack of plan for charge backs (2011)	1: Instituted plan and shared cost-recovery (2012)
Regulatory	1. The feasibility of the One State, One IRB initiative is not evident and may be too ambitious (2011)	1. Successfully implemented One CITY, One IRB and multi-CTSA master reliance agreements (2012-2013)

In 2013, we piloted a more data-driven EAB presentation with an accompanying ‘brief’. This provided members with historical trend data (indicators/metrics) and evaluation summaries on primary intended and unintended outcomes achieved. This was well received by EAB members and will be the format in which data is shared with the EAB going forward. Regularly used dashboards utilized by CTSI programs/services and leadership will be shared with the EAB. In the next five years we will work to enhance our evaluation work and build upon successes and infrastructure formed in the past five years. Our continued use of nested logic models and data collection plans (see appendix for macro level CTSI logic model and data collection plan) will work to outline the complexity, yet synergistic relationships and common outcomes that exist between the myriad of services and programs CTSI offers. Component specific outcomes and metrics are outlined within the respective component sections (Research Expertise and Methods, Research Implementation and Participation, and Network Resources and Optional Modules).

Given the age of CTSI and the nature of the CTSA national consortium, the use of comparison groups may be feasible in the next five years. Inter-CTSA comparison groups may be used to better measure the impact of innovative strategies within our CTSI and promote best practices across the CTSA infrastructure. We envision using a more experimental approach to measure the success of our Pilot Award Coaching Model and the impact it may or may not have on the success of awardees and the progress of their research. We will leverage our national connections with the American Evaluation Association, Translational Research Evaluation TIG and the national Community Engagement Outcomes Workgroup to further explore opportunities to integrate experimental approaches into our overall evaluation design.

COMPONENT 3. TRANSLATIONAL SCIENCE BASE. LEADS: R. SHAKER, MD AND TOM BRAY, MS

I. Biomedical Informatics Module (BMI). Lead: Bradley Taylor, MS and Jay Urbain, PhD

Goal 1. Provide our investigators with the informatics solutions necessary to be effective in translating discoveries into health improvements by creating a mutually learning "Health Care Enterprise-CTSA - eco system" that broadens the reach of our translational research engine into health systems and facilitates access to patient stakeholders in order to generate and test hypotheses and implement best practices.

In the current proposal (CTSA 2.0), we will leverage the resources and capabilities of our partner institutions by catalyzing the CTSA support to mature our Biomedical Informatics capabilities and expand our S.E. Wisconsin Biomedical Informatics Connectome (BIC). This connectome links the de-identified clinical data of our health systems in southeast Wisconsin to our existing clinical data warehouse (with the capability of a SHRINE [1] connection to other CTSA hubs) and provides unprecedented connectivity among investigators, the community of stakeholders, the Clinical Trials Office (CTO), and the CTSI/ Institutional resources and support (figure 1). We have deployed i2b2 for computable phenotype cohort characterization with over 1.3 million lives represented by our adult hospital EHR (EPIC Systems) [2]. It also integrates tumor registries (NAACCR) [3], and other longitudinal data sources all secured behind the health systems firewalls. We have obtained an IRB deferral from Children's Hospital of Wisconsin, and are preparing an internal SHRINE data-sharing network to bridge the adult and Children's health systems EHR data to be available for use by our investigators in the 4th quarter of 2015. The number of investigators using our data warehouse has increased continually commensurate to the increase in its capabilities (figure 2).

Figure 1 Biomedical Informatics Connectome (BIC)

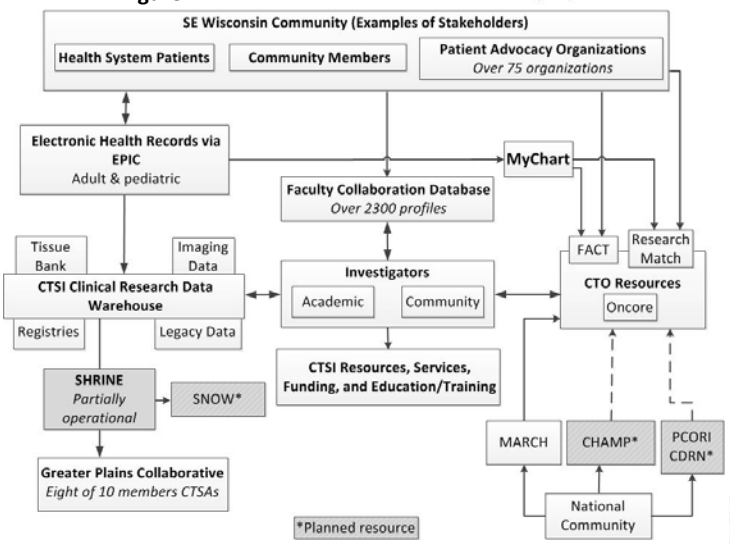
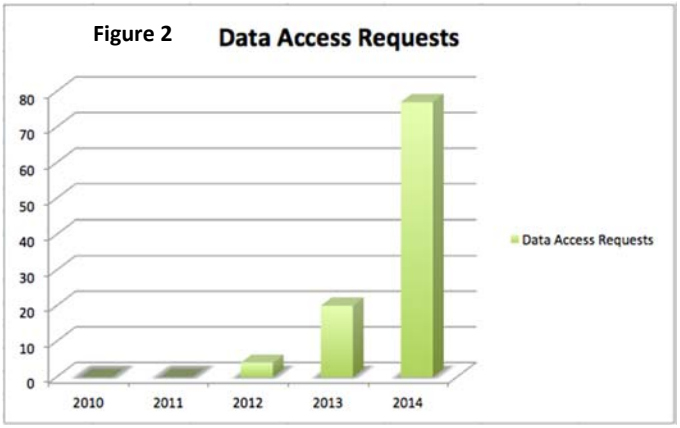


Figure 2 Data Access Requests



In order to extract clinical data for translational science, we have complemented the substantial investments in electronic health records (EHR) made by our partner healthcare systems with existing NIH-funded open source technologies (e.g., i2b2 [4], REDCap™ [5]) to provide a cost-effective common data model that promotes data transparency and interoperability with other CTSA institutions. We have developed our clinical data warehouse with the goal of data sharing regionally and nationally with other CTSAs. We currently support research management systems such as REDCap™ for registries and Oncore for Clinical Trials Management [6].

REDCap™ access is provided to the CTSI consortium to simplify the process of data collection. We continue to see a steady increase in interest and utilization of our REDCap™ resource and continue to recommend its use for both existing and proposed research projects. A process is in place to incorporate the use of common data elements (CDE's) within the registries to allow for the harmonization of instruments across institutional boundaries. We envision that appropriate data from our warehouse will be linked to national repositories.

Data Sharing and Collaboration. Our hub is a leading site of the PCORnet Greater Plains Collaborative (GPC) Clinical Data Research Network (CDRN), which is comprised of 10 academic medical institutions [7]. Eight of these ten are also CTSA hubs that create a data sharing opportunity (inter-institutional agreement signed, December 2014) for multi CTSA networking and collaborations. Our CTSA hub benefits from strong relationships with the PEDSnet CDRN and within Wisconsin, we have been working alongside our state CTSA

partners at the University of Wisconsin Madison and the Marshfield Clinic to develop a strategy for the implementation of a new statewide i2b2 resource called the SHRINE Network of Wisconsin (SNOW).

The creation of highly functioning networks across CTSA hubs will require query results with comprehensive clinical data sets that conform to standard ontologies. We have already begun harmonizing our ontologies to comply with meaningful use terminologies such as LOINC [8], RxNORM [9], SNOMED [10], ICD9 & 10 [11], CPT [12] and HCPCS [13]. These efforts will continue as one of the goals of the current proposal. As our healthcare system's EHR meaningful alignment continues to unfold, our approach will be incremental and iterative and in coordination with NCATS national network of Biomedical Informatics activities.

Our CTSA hub and the GPC both use the i2b2/REDCap™ platform, which allows the flexibility to assimilate multiple disparate data sources. This provides a low cost, open and reusable platform that can reliably integrate patient-level data collected for clinical registries and specific research projects. Dr. Jay Urbain, the Co-Director of the Biomedical Informatics module, is leading our hubs collaborative efforts with the University of Kansas and the University of Pittsburgh on the development and sharing of Natural Language Processing Software Solutions. Additionally as part of our Biomedical Informatics connectome (BIC), we will continue to develop Waypoint©, a programmatic system of collecting, measuring, and reporting metrics/achievements. We are also working with the Community Engagement (CE) module to develop a registry of community partners where we will capture elements describing relationships and research focus areas to rapidly identify and match Community Based Organizations (CBO's) to academic researchers. Use of established open source NIH-funded technical infrastructure, such as i2b2 and REDCap™ along with other open source technologies provides for greater, more cost effective data transparency, enabling us to rapidly scale our capabilities as needed. In alignment with NCATS goals, the CTSI of Southeast Wisconsin routinely shares its technology, processes and creative ideas with other CTSA hubs and healthcare systems.

Data Security and Privacy. Providing access to health data for research while preserving privacy and security poses numerous challenges. In order to protect our patient population, MCW has implemented SOP's for safeguarding the privacy of the protected health information. Oversight issues such as data ownership and governance are reviewed and managed by the **Data Request Oversight Committee (DROC)**. We use data sharing and use agreements with all investigators seeking access to clinical research data. We use our in-house developed web-based tools that assist an honest broker to manage information requests from our CRDW [14]. These tools and the DROC manage the re-identification risk, easily enable the review of concepts for business sensitivity, and confirm that the hypotheses generated for a requested study is within the investigator's area of expertise. Information is only released following the review and approval by the DROC. Re-identification of data requires prior IRB approval. In order to reduce concerns from healthcare systems and as we build trust, we believe the added step of mediation by honest brokers, rather than full automation is more appropriate. Audit controls, governance and oversight have been integrated into each of these steps to ensure the security of data, and to protect patient privacy. We regularly review these policies and control systems, and adjust to meet new regulatory requirements and collaboration needs.

Research Friendly Consenting. The data warehouse can be an effective tool for identifying patients eligible for studies, particularly when oversampling subgroups, or stratifying/randomization based on demographic or clinical characteristics is needed. However, the ability to systematically alert providers in real time about patient eligibility for clinical trials, could substantially change current practice and enhance clinical trials enrollment. Integrating "Best Practice Alerts" (BPAs) directly within the EHR delivers real-time notification to clinicians during patient encounters regarding active clinical trials for which a patient may be eligible. We believe that the use of BPA's is timely and effective, and thus it is included in our deliverables for the current proposal (Table 1 next page). Furthermore, a link to our CTO's ResearchMatch© [15] and FACT ("Find A Clinical Trial," developed in-house) with enrollment capability has been activated in the MyChart module of EPIC in the adult hospital with plans for its incorporation into our pediatric health system. We plan to develop similar access for our VA patients, but recognize its inherent complexity. These services along with connectivity with CBOs and our patient advocacy NGO partner Community Health Charities, representing over 75 organizations, provide additional avenues for patients to participate in research studies. These informatics capabilities enhance the ability of Southeast Wisconsin Biomedical Informatics Connectome in assisting our investigators and patients to engage in translational research. Incorporating the recording of standardized (e.g. NIH PROMIS system) patient-reported measures such as pain, distress, and quality of life into the clinical workflow integrates research with clinical care and is another major area that we plan to address by year two of this grant cycle.

Goal 2. Develop training programs and instructional modules to equip our investigators for the most efficient use of biomedical informatics capabilities.
We currently offer a number of video tutorials and in person training sessions for a) ensuring quality and compliance and efficient access to the CRDW, and b) the creation of REDCap™ registries. We will add the following training opportunities in the current proposal: 1) self-paced guides for the use of i2b2, 2) expanded use of data without being limited to time, place or specific purpose (in consultation and collaboration with the regulatory knowledge support module), and 3) hosting monthly "lunch and learn" sessions for trainees at various levels of experience to help investigators incorporate the current Biomedical Informatics tools into their research programs. We will continue to provide multiple layers of training drawing on existing human-subjects research training programs (including CITI [16]), ensuring that investigators receive education on issues of privacy, confidentiality, informed consent, and other related issues involving human participants and/or health record data.
Participation in National CTSA Network Activities. We are committed to participate in national CTSA network informatics activities for assessment of informatics performance and goal setting across the entire CTSA community. Mr. Bradley W. Taylor, the Chief Informatics Officer for our CTSA will serve as our liaison to the network. We are committed to working toward adoption and implementation of standards and practices endorsed by the CTSA program, and sharing informatics tools and solutions developed at our hub.

TABLE 1. Deliverables	
1)	Continuation of harmonization of ontologies to comply with the meaningful use terminologies
2)	Implementation of a new statewide i2b2 resource (SNOW)
3)	Development and sharing of NLP software solutions.
4)	Continue to develop Waypoint©, a programmatic system of collecting, measuring, and reporting metrics
5)	Develop a registry of community partners to capture research interest to link to academic researchers.
6)	Integration of "Best Practice Alerts" (BPAs) directly within the EHR
7)	Link CTO's ResearchMatch© and FACT to the MyChart module Pediatric EHR
8)	Incorporating the recording of standardized (e.g. NIH PROMIS system) patient-reported measures such as pain, distress, and quality of life into the clinical workflow integrates research with clinical care
9)	Training opportunities:1) self-paced guides for the use of i2b2, 2) Consent for expanded use of data without being limited to time, place or specific purpose 3) hosting monthly "lunch and learn" sessions Data-warehouse use

Metrics. Table 2 outlines the primary outcomes, indicators, and data sources for our BMI program. Waypoint©, CTSI's centralized database will serve as the primary method in which process and outcome metrics are captured and collected. Quarterly dashboards will be used to summarize key performance measures and outcome data by core component (i.e. Translational Science Base). Dashboards and other evaluation reports will be shared with CTSI and program leadership to aid in action, decisions and discussions related to continuous quality improvement and evaluation.

Table 2: Biomedical Informatics Outcomes and Indicators

OUTCOME	INDICATORS AND MEASURES	DATA SOURCES	RESPONSIBLE PERSONS	REPORTING TIMEFRAME
Aid in the data sharing and enabling data access, integration and processing	# of investigators utilizing REDCap™ Development and support of CTSI's internal database, Waypoint # and type of research data/facts integrated into CRDW and source (CHW, etc.) # and type of individualized and group training sessions offered Creation of SHRINE Network of Wisconsin	Waypoint I2b2/CRDW	BMI, Evaluation	Quarterly and Annually
Help create a flexible, sustainable digital enterprise where digital assets are interoperable	Tools and techniques developed for NLP Implemented open source technologies # and type of clinical data sources in data repository Implementation of BPAs (# & describe, by year)	I2b2/CRDW EPIC (EHR system)	BMI, Evaluation	Quarterly and Annually
Ensure the security of study data	# of data sharing and use agreements # of studies receiving DROC approval	REDCap™/ Waypoint	BMI, Evaluation	Quarterly and Annually
Offer user-friendly research tools and solutions to aid in the success of clinical and translational research	# and type of investigators utilizing BMI tools and services (by service/tool (CRDW, image de-identification, etc.) # of data access requests and research type(s) utilizing CRDW # of investigators and studies utilizing ResearchMatch©	Waypoint	BMI, Evaluation	Quarterly and Annually

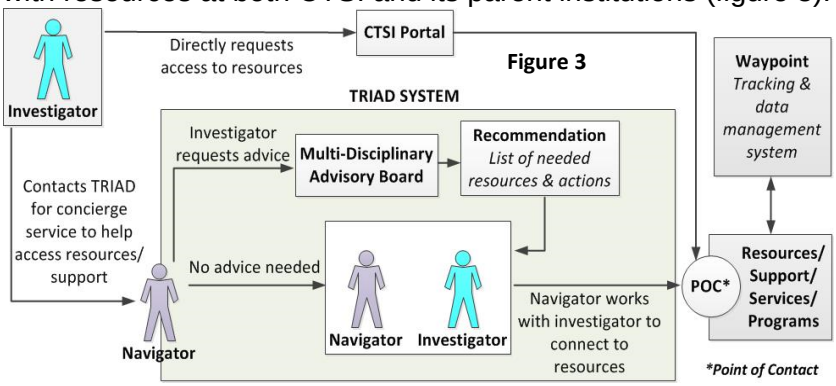
II. Collaboration and Multi-disciplinary Team Science Module.
Leads: Theodore Kotchen, MD and David Harder, PhD

Introduction. Over the past five years, our hub has made significant strides in incentivizing, facilitating and supporting collaborative inter-disciplinary teams through its nucleating pilot feasibility awards, integrating research into clinical practice grants and education/training programs. We have catalyzed the formation of nearly 90 multi-, inter-disciplinary research teams with participation of nearly 300 investigators (see Overall section). We have used a variety of methods in addition to pilot awards to assemble these teams, including our nucleating workshops, with topics chosen based on recommendations received from investigators and CTSI leadership. Table 3 illustrates some of the successes that have resulted from the nucleating workshops in stimulating collaboration among the investigators from CTSI partner institutions. These initial successes have set the course for future activities involving the community of patients and patient advocacy groups amongst others in these nucleating workshops (see CE module) [17-21]. Our CTSA hub remains committed to advancing team science and supporting multi-disciplinary research teams. We strive to catalyze convergence of various disciplines, most notably life sciences, physical sciences and engineering [18] to address important health issues through translational research. Our CTSA hub is well positioned to successfully achieve this goal. Our partner academic institutions (Marquette University, University of Wisconsin- Milwaukee and Milwaukee School of Engineering) bring tremendous intellectual and laboratory assets in physical sciences and engineering to the hub, while MCW provides a remarkable cadre of experts in biomedical sciences along with its significant NIH supported research enterprise, all complemented by our three health system partners enabling performance of clinical and translational research. **These are our goals:**

Table 3. Accomplishments of Collaboration & Team Science Successes

Collaboration & Team Science Activity	Metric
Nucleating Workshop	11 workshops with 1039 Attendees, Catalyzed development of 20 pilot feasibility grants 49 New Interactions on Collaboration Continuum
Collaboration Continuum[4]	Co-Existence = 5 Networking = 14 Collaboration = 24 Coordination = 5 Coalition = 1

Goal 1: Create an additional system to help guide teams and investigators to resources and support. Investigators and teams often encounter difficulty identifying and accessing resources and navigating the research enterprise. The CTSI is creating the Translational Research, Innovation, Acceleration and Development (TRIAD) service to help research teams and investigators navigate the processes and connect with resources at both CTSI and its parent institutions (figure 3).Two TRIAD *research navigators* will be assigned to serve the partner institutions as a point of first contact for those seeking CTSI's assistance. Using a case management approach, the navigators will communicate with investigators, assess their needs and connect them to appropriate resources. These research navigators, along with the community navigator (see CE Module) and participant recruitment facilitators (see NRO) form a collaborative network which will link investigators to the community of stakeholders and the patients.



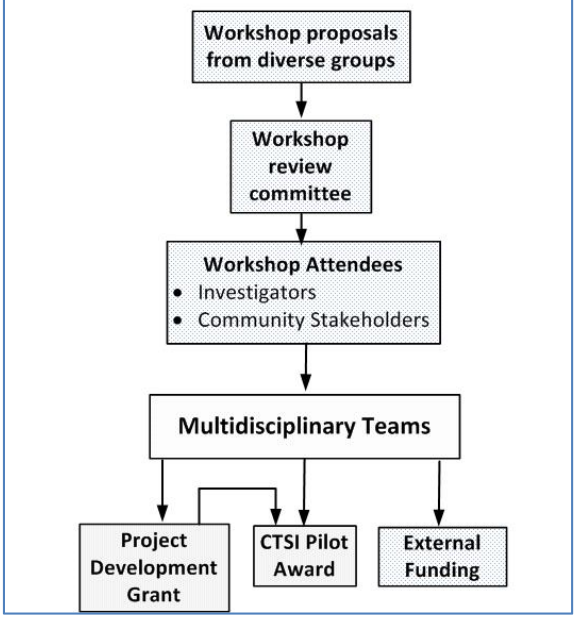
For investigators and teams who want comprehensive assistance beyond use of resources, TRIAD will provide a Multidisciplinary Advisory Panel (MAP), consisting of experts in Bioinformatics, Biostatistics, the Clinical Trials Office, Regulatory, Community Engagement and other areas as appropriate. The navigator will prepare a detailed proposal in collaboration with the investigator which addresses the investigator's plans and current progress. The advisory panel will review the proposal, meet with the investigator and issue a set of recommendations; a "personalized roadmap" identifying tasks the investigator should complete and resources or people with whom the investigator should connect. The navigator will help the investigator make the connections and will follow-up on their progress over time. This concierge service will complement our existing access system *via* our portal/ website. In the past five years, we have identified, categorized and developed access points as well as a cost structure for our hub partner institutions, core facilities and services, including utilization of hospital equipment and services. We also have completed our faculty collaborative database, which currently includes 2,300 profiles from all our partners. Our Community Engagement module and

Biomedical Informatics program are in the process of developing linkage to CBOs, patient advocacy groups and other community resources to facilitate engaging community stakeholders in the translational process. Our Biomedical Informatics connectome houses and operates all these resources and information and will be instrumental in supporting our translational research teams.

Goal 2: Develop a mechanism for tracking utilization of resources and expertise. Through a catalog database, TRIAD navigators will familiarize themselves with institutional resources and how to access them. TRIAD will cultivate and grow a horizontal points-of-contact (POC) network, i.e. people who know of resources and expertise within different programs across multiple institutions. It also will connect vertically with institutional leadership and offices of research in partner institutions through CTSA leadership to address issues and suggest improvements. TRIAD also will be helpful in facilitating our LEAN process as they encounter bottlenecks and inefficiencies, Navigators will meet biweekly to share experiences and exchange information about resources and inter-institutional expertise. We are in the final stages of completing a Biomedical Informatics system called "Waypoint©" (discussed throughout this proposal) that will be used to house and organize information and to inventory resources and inter-institutional expertise at CTSI institutions. Waypoint© also will allow the tracking of teams and investigators throughout the research process, thus assisting TRIAD in spotting bottlenecks, offering appropriate resources and gathering and disseminating metrics and feedback.

Goal 3. Nucleating workshops to facilitate team building and community engagement: aligning workshop topics with interests of stakeholders. During the initial CTSA project period, we presented a number of workshops targeting specific health topics, with the primary goal of developing and facilitating multidisciplinary research collaborations around those areas. These workshops increased opportunities to involve a more diverse group of stakeholders, thus expanding team diversity. The mechanism is now in place to invite and include our community members (though our science café), our patients (through MyChart link and patient advocacy groups who collaborate with our hub) as well as other appropriate participants (see CE module). Proposals will be solicited four times yearly for workshops from stakeholders. The content of the proposals requires identification of the potential audience and speakers, a description of how the workshop will build collaborations, and a proposed workshop planning team. These proposals will be reviewed by an ad hoc workshop review committee appointed by the Executive Committee of the CTSA hub. This ad hoc committee will select the proposals with the greatest potential to generate inter-disciplinary collaborations, which maximizes community engagement/integration.

Fig. 4: Research Team Formation Through Workshops



Inter-disciplinary teams that evolve as a result of a workshop will have the opportunity to apply for a CTSI Proposal Development Grant (PDG) (figure 4). An RFA for a PDG will be announced during each workshop and will request proposals on the workshop's topic to be submitted within 6 weeks. The merit of these proposals will be reviewed by the original ad hoc workshop review committee, and outstanding proposal(s) will receive up to a $5,000 mini-grant/voucher valid for six months for CTSA services to develop a research proposal directed at a specific intramural RFA or extramural funding (NIH, NSF, etc.). An intramural or extramural proposal must be submitted within 6 months from awarding the PDG. In order to facilitate the progress of the PDG, a TRIAD navigator will be assigned to the group as a condition of funding.

A second approach to forming and fostering inter-disciplinary teams from workshops is using data gathered from workshop attendees during the registration process to coalesce proposal development teams (PDT). This approach is in response to our observation that many workshop attendees remain unconnected to a team after a workshop. The ad hoc workshop review committee will use workshop registration data to identify individuals with common interests and invite them to a PDT meeting. This meeting will follow the workshop and will be chaired by a TRIAD navigator who will facilitate the group in identifying areas of research that involves members of the group. The

objective of forming these PDT will be to generate a proposal for intra or extramural funding. The navigators will direct PDTs to the TRIAD advisory panel for advice, and progress will be documented in Waypoint©.

Six months following each health topic workshop, the ad hoc workshop review committee will prepare a workshop outcomes report (WOR) to be shared with all stakeholder agencies and the CTSI executive committee, which will include workshop evaluations and a preliminary progress report toward developing PDGs and PDTs teams that result from the workshop. The report data will be generated by the Biomedical Informatics component using Waypoint©. These results will be shared with the Quality and Efficiency component that will identify key predictors of achieving the workshop objectives and germinating deliverables from PDGs and PDTs. We have also utilized an approach called, "Integrating Research Into Clinical Practice" (IRICP), which encourages clinician scientists to formulate a research project based on clinical needs to be addressed by a multi-disciplinary team. This project has been supported by our clinical practice group for the past two years. Both this and the workshop-generated team approach will continue in CTSA 2.0 enabling us to apply our 5 years of experience to improve team formation, team operation, and its success. A number of important team development issues have been identified and mechanisms for remedying them have been developed (figure 5).

Figure 5. PROBLEM	SOLUTION
Identifying a team project that tangibly addresses a health topic	Use of nucleating workshops
Identifying potential collaborators	Development of and easy access to faculty database of partner institutions
Aligning complimentary programs among partner institutions to address major health issues through team science, which affect special populations in our region	▪ Use of strategic planning to identify and catalyze program development EXAMPLE: CTSA catalyzed a regional traumatic injury rehabilitation initiative that is progressing with minimal CTSA financial support ▪ Education and training programs focused on team science

Metrics. Table 4 outlines the primary outcomes, indicators and data sources for our Collaboration and Multi-disciplinary Team Science core. Waypoint© will be used to capture and report data, as previously described.

TABLE 4: OUTCOME	INDICATORS AND MEASURES	DATA SOURCES	RESPONSIBLE PERSONS	REPORTING TIMEFRAME
Offer research services and support that aid in the success of clinical and translational research	Catalog of regional resources and expertise (# and type of resources available) # and type of investigators connected with resource or expertise # of investigators connected to potential collaborators # of investigators assessed by advisory panel Investigator satisfaction with services received # and type of consults provided	Waypoint	TRIAD, Evaluation	Quarterly and Annually
Identify and reduce roadblocks to team science	Tenure and promotion committees recognize team-based contributions Identification of team-science values by organization Cross-hub collaborations (resources shared)	REDCap™ survey Waypoint	TRIAD, OREC, Evaluation	Quarterly and Annually
Facilitate team science groups through regularly scheduled health topic workshops and team science support (TRIAD)	Number and diversity of stake holders within and outside of the 8 CTSI organizations Number and content of workshop proposals submitted Number and content of workshops sponsored Number and type of workshop attendees Quality of workshop to achieve program objectives through attendee follow up surveys Number of Proposal Development Grant proposals submitted and funded - number of CTSI special topics proposals submitted and funded Number and type of PDT Number of PDT that submit a proposal Number and $ amount of projects stimulated through CTSI PDTs Number of deliverables from projects stimulated through CTSI PDTs (manuscripts, presentations, new grant applications for extramural funding, student involvement, clinical protocols, patents etc.)	CTSI Website Waypoint REDCap™	TRIAD, OREC, Evaluation	Quarterly and Annually
Identify and promote characteristics of successful interdisciplinary teams	Workshop evaluations from attendees Predictors of deliverables (progress along Frey's collaboration continuum, proposals, grants etc.) from PDGs and PDTs Data mined via TRIAD research navigators	REDCap™ Waypoint	TRIAD, OREC, Evaluation	Quarterly and Annually
Educate and support investigators through the commercialization process	Number of POC projects funded Number of papers published and patents filed Number of funded projects marketed to industry Number of agreements executed with industry Number of follow-on funding or grants, e.g. SBIR grants Number of industries and CTSI members attending 'Industry Days' Number of regional industries engaged as partners and sponsors Number of follow-up meeting with industry Number of video modules, additional materials produced (# of views over time) Educational alliances formed with other TTOs/ CTSAs	Waypoint CTSI Website	TRIAD, RDDRI, RIPCN, OREC, Evaluation	Quarterly and Annually

III. Community Engagement Module. **Lead: Syed Ahmed, MD, MPH, DrPH, FAAFP**

The CTSI Community Engagement (CE) Program has successfully worked with stakeholders on a number of initiatives to lay the foundation for meaningful community engagement.

Table 5: Community Engagement Accomplishments	
Leverage	$4M awarded, $8.5M Proposed
Dissemination	38 publications, 103 presentations, Discovery Radio 30,000 listeners
Education	CEnR course, 26 Science Cafes, 6 workshops, 78 SMART teams

Table 5 summarizes these achievements. Despite our progress, CTSI resides in the City of Milwaukee and SE WI where significant health disparities persist in our communities. Nationally, Milwaukee is the most segregated city by race and socioeconomic status (SES) [23]. The CTSI is a leader in developing and disseminating approaches to CE [24-27] from our educational programs aimed at faculty, community members and youth, to collaborating in community-led, team science research. The 2013 Institute of Medicine (IOM) Report defined communities to include nonprofit or industry entities engaged in translational research, disease advocacy groups, local health providers, community-based organizations, culturally defined groups, and other national or local communities [28]. The CTSI CE Program is committed to the IOM vision of integrating novel practical approaches in promoting and increasing active and substantive community stakeholder participation throughout all stages of translational research, in order to expand our capacity in successfully engaging a more diverse population that spans across sectors and communities.

The goals of the CTSI CE Program are to: 1) promote meaningful community involvement in all stages of translational science research not only at the T3-T4 levels but also T1-T2 (figure 6 next page) from project inception to dissemination, 2) increase in/outreach capacity through CE Connectors (Table 6), 3) solidify a standardized mechanism for academic policies into promotion and tenure. [29] Develop theoretically-sound, culturally-competent training, CE Consultation Services and Community Translational Pathways, and 4) disseminate best practices, highlighting effective approaches in an experimental, data-driven fashion by traditional means (publications, presentations) and through direct feedback loops in communities.

Table 6: Community Engagement Connectors and Outreach Capacity

CE Connectors	Community Outreach Capacity
MCW CHCR (Family & Community Med)	90+ funded, long-term community-academic partnership projects focused on health disparities throughout SE Wisconsin and the State over the last decade. 350 non-profit, government, and academic partners. Saturday Free Clinic for the Uninsured.
Nonprofit Center of Wisconsin	350 nonprofit member organizations, hundreds of non-member nonprofits, more than 40 corporate members of the Business Volunteer Council, and thousands of individuals each year.
Community Health Charities of WI	1500 businesses, and 80 member charities, including: charities including the American Cancer Society—Midwest Division, National Kidney Foundation of WI, March of Dimes Foundation, and the Alzheimer's Association—Southeastern WI.
Community Health Clinics	Gerald L. Ignace Indian Health Center; Aurora Walker's Point Community Clinic; Proyecto Salud; CORE El Centro; Lisbon Avenue Health Center; Sixteenth Street Community Health Center; Isaac Coggs Heritage Health Center; Marquette University Clinic for Women and Children; Muslim Community & Health Center of WI
UWM CCBLR	209 nonprofits, schools throughout the Metro Milwaukee Area. UW-Milwaukee places approximately 1,500 students each semester through courses with a service learning component at local non-profit agencies.
Community Health Advocacy	Milwaukee Center for Independence; Pink Shawl Initiative; Milwaukee Jewish Foundation; Penfield Children's Center; United Community Center's Elder Care Program; Urban Indian Wellness Consortium; Milwaukee Latino Health Coalition; Electa Quinney Institute; Dry Hootch of America
Government (State of Wisconsin)	Wisconsin Department of Health Services; Health Department: City of Milwaukee, West Allis, Wauwatosa

We believe that to best improve and expedite translation of research results into positive health outcomes, meaningful community collaborations must occur. Scientific teams must be equipped to approach complex health issues through understanding and applying theoretically sound principles of community engaged research. Otherwise, important discoveries fail to impact all communities, individuals across the lifespan, the health disparate and/or disabled because interventions are not adapted to be culturally appropriate, relevant, and accessible. Recognition of the communities' role in CE research is the first step in a truly applied CE research enterprise; a next step is providing a platform by which communities partake in research design from concept inception, actualization, team collaboration, recruitment, and knowledge dissemination. Community's role in community engaged research will vary depending on T levels (figure 6 next page) (the community may assist at all T-levels by identifying community health needs, but may be a host site for T3-T4 research).

Goal 1. Promote meaningful community involvement.

This proposal was formed through ongoing input and evaluation processes from a wide array of existing stakeholders (Table 7) in a manner which embodies the Principles of Community Engagement.

Figure 6 Communities' Role in T1-T4 Research

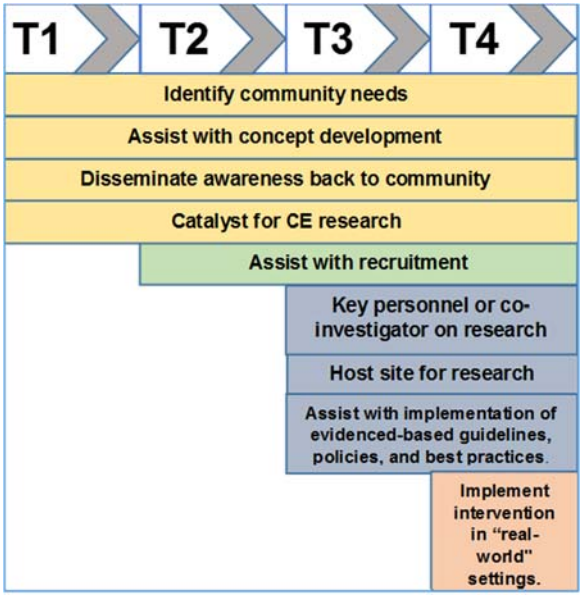
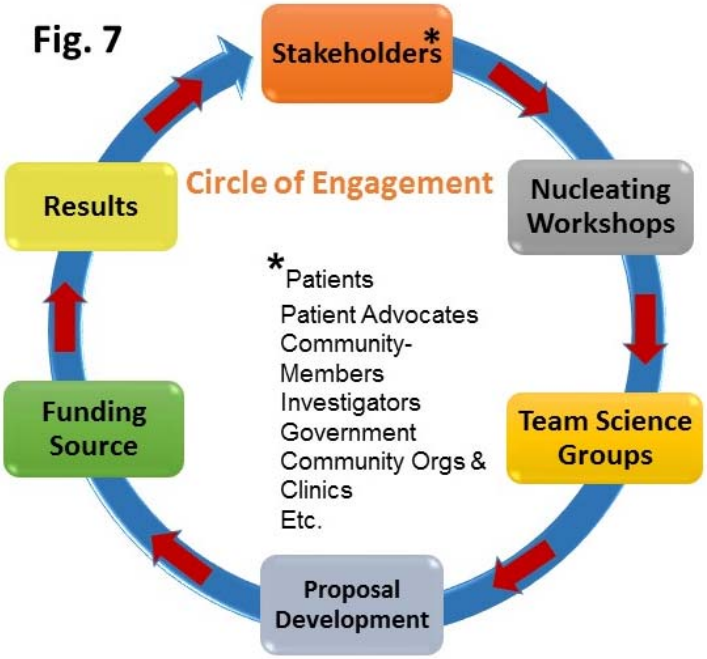


Table 7. CE Program Stakeholder Inputs

CTSI of SE Wisconsin	Community Stakeholders	Knowledge and Planning
• Institutions, Faculty, Clinicians, Staff • Existing Infrastructure • External Advisory Board • Citizen Advisory Council • CTSI Members	• Health & Social Services • Public Health Lab • School Programs • Coalitions • Advocacy & Faith Groups • Industry	• Science Cafes • CEnR Conferences • CEnR Course • CE Think Tank with T0-T4 • CTSI World Café • Carnegie Classifications

For example, in 2014, CTSI held a World Café (30) consisting of regional strategic planning sessions with over 400 individuals from health care, research, academic, nonprofit, business and government communities. Their input guided the creation of small concept development groups, who are committed to working with CTSI in increasing Community Engaged research.

Fig. 7



We will build upon our successful **outreach programs** and regional **infrastructure**. CTSI CE Program's Circle of Engagement (figure 7) shows a circular system designed to educate and invigorate communities to engage in translational research. This model of community education, patient integration, team science, research discoveries, outcome dissemination, feeds back into our community education programs. Initial engagement requires specific community contacts: Stakeholders will be engaged via MyChart, Newsletters and Education Workshops, MyCommunity/MyCTSI website, Science Cafés, CTSI Membership; Community Health Charities Org. membership and forums, MCW's Center for Health Communities & Research (CHCR), UWM's Center for Community-Based Learning, Leadership, and Research (CCBLR); and direct contacts (Table). A CTSI Community Navigator will directly connect with individuals and groups interested in research and direct them to Nucleating Workshops, with the purpose of assembling community-informed Science Teams that will address critical issues in translational science. These groups will utilize workshop time to formulate a research Proposal. These teams will continue to cultivate their proposal after the workshop leading to an application for CTSI Pilot Funding. Through a vigorous review process (See CTSI Pilot Translational and Clinical Studies Program), selected projects will generate pilot data which will Disseminate Findings through the traditional channels (publications and presentations) and direct community dialogue (Science Cafés, Newsletters and, Education Workshops, etc.).

Goal 2. Increase in/outreach capacity. CTSI CE Program will be strategic in outreach by leveraging existing organizations which have large community outreach capacity. These CE Connectors (Table 5) will extend our own outreach in educating, training and engaging communities in translational science research. CTSI Science Cafés will continue to support bidirectional dialogue and dissemination about health science topics but will now incorporate and facilitate direct interaction among researchers and community members in settings outside the

walls of academia. (25) Science Cafés will serve as an experiential tool for both early and late stage investigators to practice community-level education and learn to participate within an authentic, equitable dialogue. CTSI will provide a platform to bring ideas together and generate research protocols at Nucleating Workshops (see Collaboration and Team Science Module) held four times a year, where CE experts will provide advice, insight and guidance to foster mutualistic discovery and networking among scientists and non-scientists. These workshops will serve to develop understanding and identification of researchable health issues that resonate within and across several major communities. Outcomes of these workshops will be tangible research proposals ready to compete for CTSI Funding (see RIP). Through this process, communities will play a direct role in concept inception, actualization, team collaboration, recruitment, and knowledge dissemination.

Goal 3. Standardized mechanism for promotion and tenure. CTSI institutions are committed to recognizing community engaged scholarship and research as a criterion for tenure and promotion. The CTSI CE Program will work with leaders to ensure CE's place in academic policies of tenure and promotion. MCW, MU, and UWM have all received classification as a Carnegie Community Engagement institution—a distinction that names them among the nation's top universities for community engagement [31, 32]. We will leverage this membership for evolution of CE in tenure and promotion.

Increase capacity through culturally-competent training and mentoring programs**.** CE Consultation Services will dedicate expert mentoring, counsel on an individual or group level, teach in courses and at workshops, and advise councils to guide all levels of academics, and/or community organizations looking for partners and collaborators. We will address individual investigator needs by offering a personalized roadmap, including guided directions through points of intersection that contain assessment, consultation, education and/or positive reinforcement, and example's and resources along the way. Formal and informal education of students, faculty, staff, citizens, and community based organizations will impact the CE ability and activity among individuals to embody basic principles that foster trust and positive, reciprocal collaborations.

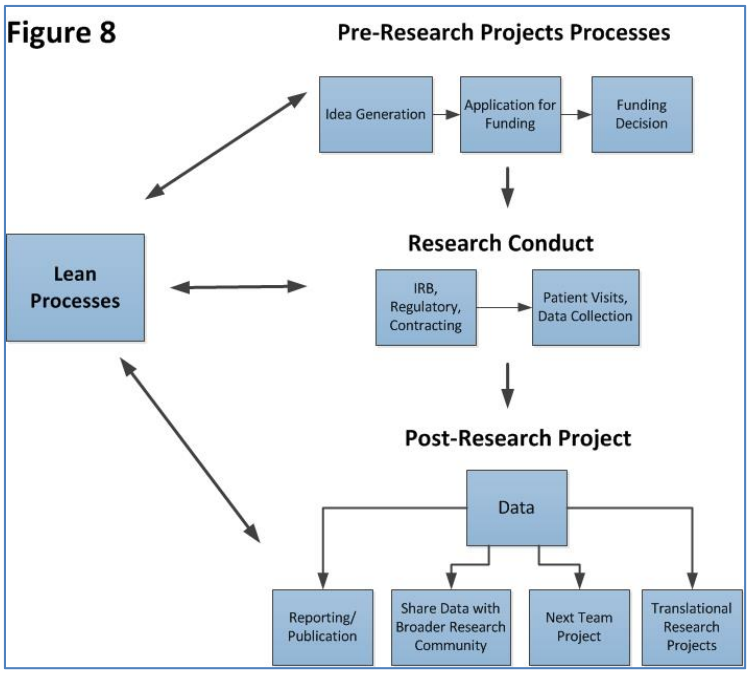
The CE Program will assist in the developing a diverse translational workforce, well trained in team science and translational/clinical research, capable of engaging the community in various aspects of their research through a multi-pronged approach including our KL2, and TL1 programs. This entails embedding informed and engaged community members, improving skills in community-academic partnership, and encouraging progressively broader segments of the community to participate in the genesis, conduct and use of health-oriented research and discovery activities [33-35]. We will create Community Translational Pathways (CTP) to provide a knowledge-based, personalized roadmap for CE education and practice for CTSI institutions and community. Capacity needs among a broad array of learners will be defined and addressed. We will define pathways and directions to best practices through education and skill building via varied experiences. Virtual and in-person support mechanisms will be established for different algorithm-based profiles which place academics and community on "roads to practice" from multiple points of entry and along a spectrum of CE development preferences from low (early learning) to high (community-academic partnership). This also will facilitate faculty development regardless of goals, from knowing why community matters, to knowledge of CTSI resources supporting CE, to actively partnering with community.

Goal 4. Disseminate best practices. A repository of CE resources will inform a virtual roadmap for various CE need profiles with customizations for end user interface. This "grid" will be developed in collaboration with the Biomedical Informatics Module and will serve directed and exploratory CE learning. Resources will include examples of projects that demonstrate best practice, information for basic cultural competency, and access to CE experts for consultations. Education and mentoring pathways will enhance CE capacity, practice and careers. Using algorithms to present suggested pathways an array of resources including interface with numerous broader CTSA proposed initiatives will be accessible via MyCommunity/MyCTSI website and Community Navigator. Investigators vary widely in their career stage, interest in CE, knowledge of CE, and experience outside academia in relation to their research. A variety of educational opportunities are necessary including practical information and guidance to basic and applied scientists on transparency and accountability when working with community to one on one mentoring and community-based experience building. Table 8 outlines the primary outcomes, indicators and data sources for the CE Program.

TABLE 8. OUTCOME	INDICATORS/MEASURES	DATA SOURCES	RESPONSIBLE PERSON/CORE	TIMEFRAME
Increase meaningful bi-directional education, research, policy, programming, and dissemination to maximize capabilities and catalyze collaborations where community is part of research.	# of users of CE virtual roadmap, types of learners (low-high); # of consults provided, by whom (capacity); # and type of CE resources in roadmap; Assessment outcomes of CE learning needs and desires; # and type of educational and mentoring activities provided; -# of individuals participating in/completing CE educational courses and programs; # of individuals mentored by CE faculty (Learning objectives (pre/post questionnaire to evaluate), Stratification of potential participant learning needs and desire, Evaluation of educational offerings, P&T involvement within CTSI institutions, Forms of "reward" for accomplishment- # certificates, "merit badges"); # Event Participants, their evaluation of learning experiences, measures for confidence, # of proposals generated and/or funded, # Collaboration measures post-connecting	Needs Assessment (tbd) Waypoint Pre/Post Assessment tool (tbd) Science Café Evaluation CTSI website	CE Workforce Diversity, Evaluation Workforce Diversity, Workforce Development	Quarterly & Annually
Increase meaningful bi-directional education, research, policy, programming, and dissemination to maximize capabilities and catalyze collaborations where community is part of research.	# of users of CE virtual roadmap, types of learners (low-high); # of consults provided, by whom (capacity); # and type of CE resources in roadmap; Assessment outcomes of CE learning needs and desires; # and type of educational and mentoring activities provided; -# of individuals participating in/completing CE educational courses and programs; # of individuals mentored by CE faculty (Learning objectives (pre/post questionnaire to evaluate), Stratification of potential participant learning needs and desire, Evaluation of educational offerings, P&T involvement within CTSI institutions, Forms of "reward" for accomplishment- # certificates, "merit badges"); # Event Participants, their evaluation of learning experiences, measures for confidence, # of proposals generated and/or funded, # Collaboration measures post-connecting	Needs Assessment (tbd) Waypoint Pre/Post Assessment tool (tbd) Science Café Evaluation CTSI website	CE Workforce Diversity, Evaluation Workforce Diversity, Workforce Development	Quarterly & Annually
Application of methods for evaluation, research, and dissemination within our CTSI and "CE hubs" nationally.	# and type of community action plans developed; Stratification/typology of community partnerships; CE support evaluations; # and type of community-academic interactions; Effective and non-effective lessons learned during stages of translational research and their impact on authenticity and degree of engagement; # and type of engagement with other CTSA CE hubs; # and type of CTSI resources shared with other hubs; Publications & presentations	HWPP Database Waypoint CE teams records	Team, SNA Consultant, CTSI Admin, Evaluation	Quarterly & Annually

IV. Quality and Efficiency Module. **Lead: Kati McCarthy, PhD and Jeffrey Whittle, MD**

Our CTSA hub has developed the initial approach to improve the value/quality of research by focusing on each of five areas identified as contributing to value by Loannidis and Khoury - *productivity, quality, reproducibility, sharing* and *translational influence* [33]. Loannidis' five component construct of ***quality*** underscores that productivity alone is only part of the equation. At the same time, experience teaches that one cannot reliably "pick the winner" in the ongoing race to identify the best approach to prevention, diagnosis, and treatment; [34-35] thus, **many** research paths must be followed until their promise – or lack thereof - is recognized; this requires attention to research ***efficiency.*** We believe that our efforts to improve research quality must proceed in parallel with ongoing programs that seek to improve research efficiency. Although the largest and central activities of the research enterprise are the research procedures themselves (figure 8), multiple additional steps are necessary; each providing opportunities to enhance efficiency beyond the opportunities that are present in the research procedure itself. Because no one researcher "owns" these additional often administrative steps, the CTSA 2.0 will take ownership of efforts to improve their efficiency.



The search for value is not confined to translational research. Indeed, management science has developed a range of approaches to ensure that an enterprise generates products of maximum value at minimum cost. These approaches have coalesced into several well-known named business strategies, each of which include a set of principles and practices that aim to promote value creation and decrease waste. While these were developed in industrial settings, they have been adopted in healthcare [36], pharmaceutical research and development [37-38] and now translational science [39-40]. We are particularly interested in Lean

management [41], as its focus on identifying value and empowering teams to identifying the value-adding (and wasteful) steps in current approaches is consistent with the highly collaborative environment that CTSI 2.0 will foster. LEAN also emphasizes the value of external (customer) perspectives; this insight permeates our approach. We will integrate these perspectives in the following specific approaches in collaboration with the Participant and Clinical Interactions and the Regulatory Knowledge and Support Modules. The approach to quality has been described in the PCI module. Our objective in this module is to promote efficiency of our biomedical research enterprise. Here our goals focus on efficiency by applying LEAN principles.

Goal 1: Applying LEAN principles to address factors that limit research quality and efficiency: There is ample expertise in LEAN management throughout CTSA 2.0 institutions. Management scientists and industrial engineers from our partner MSOE will work with Dr. Jeff Whittle, MD, MPH, a senior researcher with experience in a whole range of human research activities and quality improvement to achieve this goal. Dr. Whittle will direct these activities across the CTSA hub, providing a consistent bridge to the biomedical research community for LEAN experts.

Goal 2: Using existing processes to monitor the research cycle's speed and research quality. We will extract data from existing parts of the research infrastructure to monitor the research cycle without increasing researchers' administrative overhead. These include the linked IRBs overseeing all CTSI supported research, the Clinical Trials Office (CTO) and CTSI's Waypoint resource tracking system. These data will facilitate evaluation of our improvement efforts and provide insight into potential roadblocks. We will focus on intermediate milestones, which can be customized to identify issues at an actionable stage. For example, an investigator's estimate of the time from IRB approval until the first subject is recruited is a useful early measure of feasibility for recruitment-dependent research. Such real time data can allow the CTSI to work in collaboration with the study investigators to resuscitate or redirect a project that seems unlikely to achieve its original objectives. Because all human studies must "touch" one of the IRBs, the IRB process provides an opportunity to collect data that are tailored to that study. These tailored data are key to identifying likely bottlenecks, use of processes that CTSI may be able to accelerate by offering use of shared resources, and key points in the process where futility can be recognized.

The CTSI CTO has implemented the use of OnCore, an industry-leading clinical trials management software for all CTO studies. Within MCW, the two leading trial groups (Cancer and Cardiovascular Disease Centers) have adopted its use, and additional groups have requested access. It is anticipated that by the fourth quarter of 2015, all of the Hub's trials will utilize OnCore. While the software is intuitive, we anticipate that just as with REDCap™, the need to change processes is a barrier to use. CTSI will provide free implementation support to all investigators using OnCore. The software captures several data elements (recruitment rates, retention rates, etc.) that are standard industry practice. OnCore also captures data required for annual IRB continuing review and will be modified to include fields that describe research type and the investigator identified quality metrics. OnCore data will be monitored for meeting plan milestones (see Patient Interaction section). LEAN teams will work directly with the CTO office to identify and address bottlenecks and gaps.

Waypoint© (see Biomedical Informatics module) will provide data on the use and value of various elements of the CTSI research infrastructure, including pilot grants, regulatory, education and career development, and overall research facilitation and support through ancillary services, such as grant writing, team-building, workshops and conferences. Each one of these has a process, which can be further refined to be more efficient and effective. The LEAN teams will work in close collaboration with the hub's internal evaluator to ensure a holistic approach to improving the efficiencies and outcomes that the CTSI aims to achieve. This collaboration will also aid in identifying institutional changes required at the macro level. While the research process is the primary focus, many steps precede and follow the actual conduct of research, which affects its efficiency and quality (example: contracting, IRB, other support services, etc.). The LEAN teams will work with the hub's offices of research to improve efficiencies of these services (see Overview). A recent example of LEAN impact on efficiency was the consolidation of three independent research pharmacy services on the MCW campus (FMLH, CHW and MCW Cancer Center), resulting in the adoption of standardized common procedures, transparent pricing structure, unified systematic oversight and mutual education regarding best practices.

Goal 3: Facilitating bottom up improvement of research quality and efficiency. While we anticipate our monitoring processes will uncover many opportunities for improvement, we recognize that researchers have insights that cannot be replicated by monitoring. Our Quality and Efficiency program (Q & E) will provide on-

line access to Lean management teams that could help researchers clarify the issues that are barriers to their productivity. Dr. Whittle, who directs this effort, will evaluate initial communications from researchers and link them to the Lean expert (s) who will conduct the initial needs assessment. If the preliminary evaluation suggests the problem warrants action, Dr. Whittle can either directly allocate Lean resources to the problem or present it to CTSI Executive leadership for decision making.

Dr. Whittle also will work with management scientists to develop a case study template to describe each Lean project, including those initiated by data analysis and those generated by bottom up processes. This will include a timeline, a description of the issue, artifacts such as process maps, eventual interventions, and before/after comparisons of relevant endpoints. The case studies will be condensed into vignettes suitable for presentation to help educate our investigators and research personnel. These vignettes will be included in the semi-annual efficiency and quality rounds, as described in the Patient Interaction Module. These rounds are anticipated to strengthen our culture of quality and efficiency driven research. While these case studies have a potentially high risk for bias, we will minimize this possibility with techniques like having independent scientists interpret the original data, member checks and triangulation with other sources of information, such as annual surveys of researchers involved in Lean projects and a sample of those who did not have direct involvement that year. These steps will lead to innovative ideas and increase engagement in developing complete and accurate case studies.

Metrics

TABLE 9: OUTCOME	INDICATORS/MEASURES	DATA SOURCES	RESPONSIBLE CORE
Improve research quality and efficiency across CTSI	Bottlenecks identified; processes streamlined (describe); time saved; costs reduced/money saved; resources available to investigators to improve research quality and efficiency	Waypoint; Work logs; IRB eBridge; OnCore; CTSI Website	Q & E; Evaluation; LEAN Teams

COMPONENT 4. RESEARCH EXPERTISE AND METHODS. LEAD: JOHN MEURER, MD, MBA

I. Translational Research Workforce Development Module. Lead: Jane Kotchen, MD, MPH

The overall goal of our workforce development program is to cultivate and train an expanded and more diverse translational research corps that can address complex health-related problems through innovative approaches and team science. Our strategies include individually tailored educational programs, didactic coursework, opportunities for trainees to participate on multidisciplinary research teams, exposure to expanded networks for training that include exposure to industry and input from patients and representatives of community-based advocacy groups. The proposed training efforts will build on our current successful CTSI instructional and career development programs, as well as incorporate additional existing opportunities for expanded training.

Current programs which serve as foundations for the proposed workforce development.

The MS in Clinical & Translational Science (MS in CTS) and the Dual MD/MS in CTS Programs are focused on the development of research-related skills through rigorous coursework in biostatistics, study design, translational research, clinical trials and best clinical practices, bioethics, research seminars and a mentored research project. Our Certificate in Clinical Translational Science utilizes some of the MS courses to provide training for individuals, such as clinical research coordinators and others who seek more abridged training that enhance their participation in translational research. Our PhD in Basic and Translational Research (PhD in BTR) is a highly innovative program that provides the opportunity for graduate students in basic science to pursue additional coursework in clinical and translational study design. Our MS and PhD Degrees in Clinical & Translational Rehabilitation Science (CTRS) are cutting-edge CTSI supported, Marquette based programs. The PhD program provides advanced education and intensive mentored translational research training to qualified non-medical professional degree holders.

Our CTSI also has two career development programs for faculty engaged in translational research. The Clinical Research Scholar Program (CRS) is a 2-year research career development program, modeled after NIH K30 and is geared towards promising junior faculty in nursing, medicine, physical therapy, engineering and social sciences and allied health at all CTSI partnering institutions. The mainstay of the program is its focus on each Scholar's mentored research project. The CTSI Mentored Clinical Research Training KL2 Program is detailed in the KL2 proposal. (See Table 1 for summary of trainee outcome).

Table 1. Summary of Trainee Outcomes

Program	Enrollees	Graduates	Publications	Grant #	Grant Funds
MS in CTS	70	59	222***	*	*
PhD BTS	19	3	24	2	$62 K**
MS/PhD CTRS	27	1	5	3	$87 K**
CRS	28	91	220***	46	$6 M
KL2	17	12	130***	23	$5.8 M

*Information not available ** Includes support from mentors' grants
*** Not mutually exclusive due to multi-program participation

We plan to develop "Pipeline Programs" grounded in those existing high school and college preparatory programs in southeastern Wisconsin that will provide opportunities for the CTSI to extend and expand its outreach in order to orient, educate, and guide an expanded cadre of individuals to consider and prepare for careers in clinical translational science. The population of southeast Wisconsin is racially and culturally diverse, and a majority of these programs are designed to augment the academic performance of individuals from disadvantaged backgrounds. These programs include: *Project Lead the Way STEM*, used in 139 Milwaukee high schools; *Students Modeling a Research Topic (SMART*), an MSOE high school science program; *MU and UWM Upward Bound Programs* that provide college readiness for disadvantaged and minority high school students; *Milwaukee Area Health Education Center Youth Health Service Corps*, a health career recruitment program which engages high school students in training projects that address community health care needs; and *Summer Program for Undergraduate Research (SPUR, which)* supports undergraduate college students for intensive summer research experiences, several SPUR students have been CTSI-supported.

Our Goals are:

1. Develop and implement curriculum and training that explicitly addresses multidisciplinary team science.
    a. Provide opportunities for trainees to learn from community, patient stakeholders and industry.
2. Develop and implement individualized training curriculum tailored to the needs of the trainee.
3. Expand the diversity of the potential trainee pool with regard to scientific discipline, skill level and cultural/ethnic background.

a. Develop translational research and best clinical practices learning modules for clinical practitioners.
b. Sponsor translational research continuing medical education (CME) opportunities for physicians.
c. Develop tutorials that familiarize community engagement stakeholders with translational research.

4. Provide expanded training opportunities and better integrate training efforts to avoid wasteful duplication.
   a. Participate in the Translational Training/Education "Collaboratory" (TTEC) with 5 other CTSA hubs.
   b. Utilize exceptional courses/training modules developed by other hubs and organizations.
5. Evaluate programs using established metrics to measure programmatic and trainee success.

Goal 1. Team science training. Our goal is congruent with the recent IOM recommendations to emphasize team science in research training [1-2]. This objective will be achieved through didactic coursework that addresses competencies essential to participation in multidisciplinary teams, which encompass specific attitudes, knowledge and skills [3]. Our CTSI hub proposes to:

a. Expand the multidisciplinary team involvement of graduate students (i.e., MS in CTS, medical student participating in the Translational Research Pathway, PhD in BTS, PhD in TRS, TL1). This will be accomplished through: 1) emphasis on team science competencies in coursework (e.g. case studies), 2) students from diverse fields participating in team problem-solving, 3) thesis oversight committees including mentors with appropriate diverse backgrounds, and 4) selection of research projects that involve some input from other disciplines.
b. Emphasize multidisciplinary teams in research career development programs for junior faculty (i.e., CRS and KL2). In developing the individualized career training plan for trainees, mentors will work with trainees to identify opportunities to participate in team research.
c. Include disease-related stakeholders/community members in training. Working closely through our robust community engagement activities to accomplish this plan. When appropriate, a community member, a patient, patient-family members or members of disease advocacy groups will be invited to participate in training by participating in didactic presentations, serving on educational advisory committees or serving on mentoring teams to guide research.
d. Include industry as a partner in training. Innovative proposals to establish short internships or consulting opportunities for trainees are described in the TL1 and KL2 proposals. In addition, there are opportunities for individuals from industry to participate in didactic courses. Our hub has unique relationships with industry, and we propose to engage these key individuals in planning for expanded collaborative training therein.

Goal 2. **Individualized training.** Time spent in research training needs to be systematically structured and depends on the learner's level of knowledge, prerequisite skills and experience in the conduct of research [4]. For early phase learners, the training and experiences are more prearranged, accommodating personal interests as much as possible. For more advanced staged learners, research training must be individually tailored for coursework and mentoring in order to meet the needs of the individuals. Over the next five years:

a. We will adapt an online assessment tool [5], and individualize the curriculum by delineating the knowledge and skills needed by each trainee [6] (see detail in KL2 proposal).
b. All students will receive advice that identifies ways in which to engage in research team experiences.

Goal 3. Expand the diversity of trainees. We will increase diversity among trainees through the following:

a. Training opportunities will be promoted across institutions through correspondence with key personnel (program directors, department chairs, research offices, etc.), provide information on the website about accessing and applying for training opportunities, and brochures/promotional information.
b. Identify and recruit under-represented minority (URM) trainees by working with the community engagement module, translational workforce diversity committee and recruiting medical student URM applicants for the dual MD/MS in CTS program (8% of the medical school first year class are URM).
c. Develop a translational research learning module for clinical practitioners in collaboration with the TTEC (see below). This will be created to meet the learning needs and enculturate value, support and engagement in translational research by non-research clinical faculty and healthcare personnel. Our hub learning, technology and design centers at UWM, MU and MSOE will assist with instructional strategies.
d. Provide faculty advisor to assist early pipeline students to learn about and appreciate CT research. We plan to leverage an MCW Advancing Healthier Wisconsin grant involving a Hispanic community

organization and CTSI partnering institutions to develop a health education program for URM high school students.

Goal 4. **Expanded training opportunities.** We propose to:

a. Develop a "Translational Training/Education Collaboratory" (TTEC) that involves 5 CTSA's (UW Madison, U. Indiana, Mayo Clinic, Ohio State, U. Minnesota, CTSA hubs) to share unique programs and also to develop collaboratively new programs as needed to avoid redundancy and duplication (see letters of support).
b. Collaborate with Harvard University CTSA to access remotely the Catalyst education courses and symposia.
c. Share faculty among the CTSI partnering institutions in educational and training activities, through cross institutional mentoring, sharing of specific lectures and seminar presentations, and access to specific training resources (e.g. patient resources, databases, etc.).
d. Provide "hybrid" course offerings that allow some learners to participate as graduate students and others to participate as non-academic program attendees.
e. Offer courses in "Good Clinical Practices" (GCP) for translational researchers and personnel.

Goal 5. Evaluate programs. Table 2 outlines the indicators and data sources for evaluation. Waypoint©, a CTSI database, will serve as the primary method used to capture and house data. REDCap and the Graduate Tracking Survey System (GTSS) (see evaluation) will be used to collect data.

TABLE 2. OUTCOME	INDICATORS/MEASURES	DATA SOURCES	RESPONSIBLE PERSONS	TIMEFRAME
Continuously develop a translational and team science workforce	# Participants completing programs & their evaluation of the learning experiences (describe participants e.g., background, discipline, etc.) Competency changes in key program outcomes (by edu program)	GTSS Waypoint CRAI	TWD team, Eval	Quarterly & Annually
Increase the number, diversity, & effectiveness of cross-disciplinary research teams	# Participants completing programs & their evaluation of the learning experiences (describe participants e.g., background, discipline, etc.) % of URM's participating in CTSI educational and training opportunities Outcomes of research teams: Publications (collaborators and nature); Grants (collaborations and nature); Technology transfer products; New discoveries & policies changed; FDA-approved drugs; Study outcomes of research benefiting from CTSI	GTSS Waypoint	TWD team, Eval	Annually
Expansion of educational opportunities available to those in SE Wisconsin	# of educational programs offered; # and nature of other CTSA educational resources offered; # & type of individuals participating in MARCH educational programs; # of GCP trained researchers relative to # of research staff on protocol; # & type of participants in Harvard education programs	CTSI Website Waypoint GTSS	TWD, Eval	Annually

Where appropriate, we will utilize common instrument (e.g., CRAI) to measure individual and program level outcomes as it relates to clinical translational research training.

Training innovations include: Multidisciplinary mentoring to provide training in team science; "Hybrid courses" that provide high quality training to a broad range of individuals who are involved in research efforts; Shared coursework among hubs and CTSI partnering institutions to avoid wasteful duplications; Inclusion of industry and community participants, patients and advocates in research training through participation in oversight committees, mentoring committees and didactic instruction; and research focus on early pipeline URM .

II. Biostatistics, Epidemiology, and Research Design (BERD) Module. Lead: Aniko Szabo, PhD

The Goals of the Biostatistics, Epidemiology, and Research Design (BERD) Module that maps onto Specific Aim 2 of the proposal are to:

1) Provide easily accessible, high quality and efficient BERD support to clinical and translational investigators through:
   a) Consultations in BERD that emphasize study design and leverage the expertise of CTSI partners.
   b) Streamlined access to consultants through the CTSI portal and TRIAD navigators, digitally tracked using the CTSI Waypoint© Database.
2) Provide BERD education and training for the translational workforce in rigorous research methods to promote best practices among researchers and minimize bias in study design and reporting.

3) Promote innovative tools and methods to address methodological gaps, and adapt or develop methods for both common and complex study design and analysis challenges in clinical and translational research.

BACKGROUND

BERD has played a crucial role in advancing and supporting clinical and translational research at our hub during the past five years. In addition to providing educational and training courses, lectures and seminars and serving on the MS thesis as well as advisory teams of our clinical scholars and KL2 investigators, BERD faculty have provided nearly 1,000 consults, helped with 330 grant applications, and coauthored over 210 publications in the past four years (figure 1).

FIGURE 1. Year	2011	2012	2013	2014 (6 mo.)
New consultations	129	284	327	216
Grant applications	84	77	94	76
Publications	59	33	62	60

Goal 1: BERD Consultations

Our hub has access to a comprehensive array of BERD expertise that will assist our investigators. MCW has 18 faculty in biostatistics and epidemiology; MU over 12 faculty in schools/departments of biomedical engineering; dentistry research; law survey center; math, statistics, and computer science; nursing; political science; social and cultural sciences; and UWM more than 16 faculty in schools/departments of biostatistics, business, economics, educational psychology, epidemiology, mathematics, nursing, public health, and social welfare. In 2015, the CTSI Executive Committee, school/department chairs, supervisors and individual faculty will agree to participate in the CTSI BERD consultation service and their availability and commitment will be continually updated in the Waypoint©. First line BERD consultative services will be provided by:

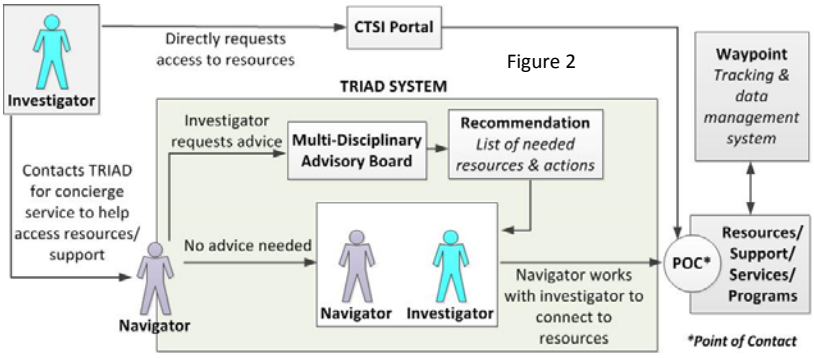
- Aniko Szabo, PhD, Associate Professor of Biostatistics, Director of the Biostatistics Consulting service in the MCW Institute for Health and Society; expertise in general clinical and translational research design
- Sergey Tarima, PhD, Associate Professor of Biostatistics
- Anjishnu Banerjee, Assistant Professor of Biostatistics; expertise in big data science and Bayesian methods
- Pippa Simpson, PhD, and Ray Hoffmann, PhD (total 0.3FTE), both Professors of Biostatistics (MCW); expertise in the design of child health studies

These consultants will provide a triage service by answering simple questions and when appropriate by referring investigators to other BERD faculty at MCW, MU, and UWM who will provide specialty consultations based on the specific expertise needed by the CTSI investigators.

BERD consultation eligible recipients: Initially BERD consultants will focus on serving primarily CTSI member investigators in the process of developing proposals for extramural funding or advancing a project to the next stage of translation. Consultants also will help CTSI pilot applicants and awardees and CTSI educational and training program participants with study design. Before initiating a study, investigators will be strongly encouraged to convert the consultation into a collaboration for questions of study design and subsequent data analysis. The expectation is that the BERD consultant will be included in grant proposals and publications related to the consultation.

BERD consultation services: BERD services will focus on planning studies, such as formulation of statistical hypotheses, optimal and novel study design, sample size calculation, randomization plan, protocol development, and statistical analyses, including collaboration in design of multi-site clinical trials with other CTSA hubs.

BERD consultation access: CTSI will provide frequent, clear communication through multiple channels to CTSI members about the eligibility criteria for BERD consultations, services available, and alternative resources for needed help. Investigators will request a BERD consultation through the CTSI TRIAD service either through the CTSI Portal/website, or in person through a TRIAD navigator. After consultation with the TRIAD leader, the investigator will be informed by email regarding their eligibility for either a CTSI mini-grant/voucher for BERD consultation or, alternate resources that are available to them (Figure 2). For voucher-eligible investigators, Dr. Simpson will evaluate pediatric requests and Dr. Szabo will evaluate all others. They will triage and refer the request to the qualified BERD consultants using a web-based list of faculty, their expertise, and availability. The BERD consultant then will either email the investigator to schedule an initial meeting or email Dr. Szabo if unable to fulfill the request in a timely fashion; in the latter circumstance, she will contact the next potential consultant. The triage and contact process information and outcomes of consults will be logged into the current MS Access database in year 1 and in the Waypoint© database starting in year 2 to capture data for metrics and outcomes noted below.



BERD mini-grant/vouchers: Based on past experience, the faculty time for statistical analysis, study design and planning including hypothesis formulation and sample size calculations averages 6 hours per project. With an hourly rate of $100 (faculty time plus admin. support), the average project will be supported by a $600 voucher. We will use these calculations to provide our investigators mini-grants/vouchers to benefit from the BERD support ($600 voucher for six hours of service). With this model, our CTSA fund will support a minimum of 330 consults, while our institutional funds will cover the educational and methodological research activities of the BERD (see budget). With the vouchers, investigators will have the choice of BERD consultant at our hub who will best meet their needs. Past investigator utilization, efficiency and quality will be factors guiding the future CTSA support for a given consultant.

Continual improvement of BERD consultation process: The consultation process will be continually evaluated for investigator satisfaction, turnaround time, and impact on grants, abstract presentations, and publications using lean management approaches in partnership with MSOE faculty and students. These approaches will enhance value and reduce waste. With the establishment of TRIAD, the relatively inefficient, past CTSI BERD drop-in consultation service will be discontinued.

Goal 2: BERD Education of the Translational Research Workforce

Sustained BERD education/training: The BERD faculty will continue to teach two biostatistics courses, serve as thesis advisors for the CTSI MS Clinical and Translational Science degree program, and mentor study design and data analysis by the Clinical Research Scholars and Mentored Clinical Research Trainees.

Innovations in CTSI BERD education: The Institute Biostatistics faculty will continue offering bi-monthly, CME-accredited BERD introductory methods lectures focusing on study design and grant development. The lectures will be combined as bundles targeting basic science or clinical researchers with recommended readings, curricula and quizzes. Appropriate clinical and translational investigators will be invited to co-present with BERD experts. The lectures will be provided as interactive classroom presentations that will be recorded and posted on YouTube for access by other hubs. After surveying CTSI members about interests and needs, additional lectures will be added to the series and presented by BERD expert faculty.

In year 1, we will plan and, in years 2-5, we will implement new, exciting methodological translational BERD grand rounds that will rotate at MCW, MU and UWM on a quarterly basis. The focus will be on common, repeated investigator problems and challenges encountered by the consulting service. The audience will be diverse BERD experts, CTSI investigators, and our other CTSI collaborators (e.g., from UW-Madison). The sessions will be web broadcast. The rounds will foster academic collaborations to write grant proposals to solve the methodological problems.

In years 2-3, we will catalyze development of several programs with the goal of increasing the quantitative knowledge and experience of our translational workforce. The innovations will include a new study design consultation shadowing program. Participants will observe the interactions of investigators and expert BERD consultants during consulting sessions to learn about the process and how to formulate research

questions and hypotheses. The consultation schedule will be posted online. The shadowing will complement the summer consultation course for MCW PhD students in biostatistics. In year 1, MCW PhD students in public and community health will be required to attend five or more consultation sessions per semester for course credit. They will discuss the observed consultations in class. The student will share ideas from class with the investigator and consultant. These PhD students also will be embedded briefly in the relevant clinical setting to learn applied team study design and to diversify their learning experience. In years 2-5, CTSI Clinical Research Scholars, other CTSI trainees, junior faculty and clinical investigators will be encouraged to shadow research design consultations (Figure 3).

Figure 3

- Year 1: focus on the consultation process, TRIAD and Waypoint, and fundamentals of study design for an audience of investigator users with the BERD consultants
- Year 2: focus on BERD and biomedical informatics including the i2b2 Clinical Research Data Warehouse with a keynote by a Great Plains Consortium leader for both consultants and investigators
- Year 3: BERD and clinical quality improvement research for consultants, investigators and clinicians
- Year 4: innovative translational methods for BERD consultants
- Year 5: current BERD needs and trends to guide future innovations and improvements.

We also will collaborate with other CTSA hubs to leverage resources and demonstrate the value of innovation. We will identify and refer CTSI investigators to another hub's online video education on how to prepare for an efficient consultation. The CTSI BERD team proposes offering an annual day-long workshop with keynote presentations from a guest speaker from another hub, presentations by local BERD experts, and small group discussions about different themes each year:

Goal 3: BERD Methodological Research and Innovation

The BERD team will promote innovative tools and methods to address barriers to translational and clinical research, and will continue methodological research supported by our past CTSA supplemental award. Examples include: methods for dose-finding trials with interval censored efficacy outcome, the use of internal pilots for observational studies, and methods for combining complex ensembles of data. Drs. Szabo, Tarima and Banerjee will perform innovative methodological translational research in internal pilot studies and complex data ensembles (see references 7-15). We will develop interim sample size recalculation methods for observational studies using different outcome types, and resampling-based adjustments to ensure desired rates of type I and II errors. In addition to theoretical developments, we will develop study templates and gather data on feasibility and investigator satisfaction in a pilot implementation of the proposed designs, also building on work in nonparametric Bayesian joint probabilistic models for complex ensembles via two-level hierarchical tensor factorizations and computationally efficient estimation procedures applicable for high dimensional data to formulate generic dependence measures for data of different types (like images and time series objects), extending the models beyond two levels, and investigating the statistical properties of the proposed methods.

METRICS AND OUTCOMES. Table 3 outlines the primary outcomes, indicators, and data sources for the BERD module. Waypoint©, CTSI's centralized database (discussed throughout this proposal) will serve as the primary method in which process and outcome metrics are captured and collected.

TABLE 3. BERD OUTCOMES AND INDICATORS

OUTCOME	INDICATORS AND MEASURES	DATA SOURCES	RESPONSIBLE PERSONS	REPORT TIMEFRAME
Provide easily accessible consultations and maximize statistical expertise in the SE Wisconsin region	# of eligible and ineligible investigators served # of projects supported # of consult hours (per visit, per month, and per quarter) Nature of consults and who provided them, i.e., capacity by CTSI partner institution # of vouchers used and unused Efficiency of consults provided as time from request to consult provided at first meeting, reported by # of days User satisfaction of service provided # of returning service requestors # of BERD consultants included in grants, abstracts, and publications Cost recovery funding	Waypoint; BERD consultants; Access database; REDCap satisfaction survey	BERD team & Evaluation	Monthly, Quarterly and Annually
Increase the number of educational opportunities available to those in SE Wisconsin	# and types of biostatistical, epidemiologic and research design courses offered per year # attending and completing courses YouTube viewing rates of online lectures # of students and scholars supported through thesis committee participation # and topic of lectures with CME credits including attendance # of BERD grand rounds, locations and topics covered # and title/type of BERD certificate and degree programs developed, and enrollment	CTSI website; Waypoint; BERD; enrollment records and course evaluations	BERD team & Evaluation	Quarterly and Annually

	# of and type of students (PhD, junior, clinical, etc.) participating in shadowing program # and topic of annual day-long workshops and attendance			
Promote innovative tools and methods to address barriers to clinical and translational research	Type of innovative methods developed Gaps in expertise in methods identified for the region and for nation # of other CTSI partner statisticians engaged Methodological problems discussed during grand rounds # of publications on novel methodological approaches	BERD program; Waypoint; CTSI Website	BERD team & Evaluation	Quarterly and Annually

III. Regulatory Knowledge and Support Module. **Lead: David Clark, PhD**

RESEARCH STRATEGY

Our overall aim is to facilitate regulatory knowledge and compliance related to clinical and translational research in conformance with IRB policies, state laws, and federal regulations in order to enable our CTSA hub to engage in regional and national networks for the conduct of multisite studies. We will achieve this aim through following six goals:

Goal 1. Innovate at all CT research levels. The Milwaukee metropolitan area "One City One IRB" alliance will expand its scope to include both collaborative medical record review studies and social/behavioral science studies across the alliance under the oversight of just one IRB on behalf of all institutions. The alliance also will expand its size by recruiting other academic institutions and medical groups in the southeast Wisconsin, the Fox Cities, and the Green Bay area. The Fox Cities are twenty communities in the greater Appleton area along the Fox River in East Central Wisconsin, one of the state's fastest growing areas with more than 236,000 residents. Green Bay in East Central Wisconsin is the third largest city in Wisconsin with a metropolitan area of more than 300,000 residents. [Timeline: 4 years]

Goal 2. Harmonize/share education resources with other CTSAs. Throughout 2014, MCW IRB's Chairpersons and senior regulatory staff have been collaborating to develop an advanced course on IRB member roles and responsibilities for experienced IRB members. The course is designed for persons with at least three years of experience serving on an academic medical center IRB, and who are already demonstrably knowledgeable about the DHHS and FDA regulations and guidance on human research protections.

The individual lessons are organized into three over-arching domains: (a) individual member skills (e.g., in-depth understanding of how to interpret and apply the regulatory criteria for approval; articulating reasons for deferring approval so that investigators are likely to understand and respond appropriately); (b) group process skills (e.g., optimal preparation for meetings; ethical decision-making); and (c) IRB consistency, policy-making, and reasons for exceptions. Most of the lessons are punctuated with videotaped excerpts of IRB deliberations, and are accompanied by a final examination and recommended discussion points. The course is offered as a web-based training tool, as a foundation continuing education requirement for MCW IRB members and available to all other CTSAs at no charge. [Timeline: 3 years]

The CTSI will unify teaching/training efforts across the eight local CTSI partner institutions to offer a single, uniform Research Integrity / Responsible Conduct of Research (RCR) training program satisfying NIH and NSF requirements for students and trainees receiving support through training, career development, research education, or dissertation awards. NIH advises that "online instruction is not considered adequate as the sole means of instruction" and face-to-face training is required. Instruction must involve at least eight substantive contact hours between the trainees/fellows/scholars and the participating faculty. RCR training includes the following areas: human subjects research, animal subject research, mentorship, collaboration, publication/authorship, data management, peer review, conflicts of interest and commitment, and research misconduct (fabrication, and plagiarism). [Timeline: 2 years]

Goal 3. Coordinate to avoid duplication. A single IRB application will suffice for implementing a clinical trial at both the adult hospital (Froedtert) and the Veterans' Administration hospital. VA protocol registration forms will be modified and incorporated into the MCW IRB application (eBridge) software. From this entry point, the clinical trial application will be routed to one of the MCW IRB Committees duly credentialed by the VA, and thus able to review on behalf of both MCW/Froedtert and the Zablocki VA sites. [Timeline: 18 months]

The MCW/Froedtert and Children's Hospital of Wisconsin IRB programs will merge to eliminate separate IRB application forms/processes and separate IRB policies. The groundwork for this merger has been

under discussion by all three institutions and the CTSI for nearly two years. Since the MCW/Froedtert IRB is already AAHRPP accredited, already includes IRB members with a broad variety of pediatric expertise, and since all Chairs and members are already trained in the application of DHHS and FDA criteria concerning the inclusion of minors/children in research, this initiative requires a focus on logistics and manpower. The current MCW/Froedtert IRB application already includes all the questions and criteria necessary for reviewing pediatric studies. Importantly, the MCW/FH IRB will add an all-pediatric committee to its roster for the review of most more-than-minimal risk research. [Timeline: 3 years]

The CTSI will offer a Good Clinical Practice training course for investigators, study coordinators, and study staff at all eight partner institutions (we will adopt the course suggested by NCATS when available). This course will be dovetailed with institutional requirements for research (e.g., data retention policies, data encryption policies) and be a mandatory requirement for all engaged in any type of clinical trials. [Timeline: 3 years]

Goal 4. Demonstrate innovation. The "CTSI Passport Initiative" will advance from its original goal (a mechanism for helping study teams satisfy all the requirements for implementing a study in either the adult or children's hospital) to a mechanism for helping any study team satisfy all applicable institutional requirements for implementing a study in any of the eight CTSI partner institutions and/or all Consortium partner institutions.

Beginning in January 2015, with private foundation support, the MCW IRB will develop, pilot, and promulgate human subjects protection training courses for community organization partners that will substitute for mandatory training requirements designed for academics (i.e., Collaborative Institutional Training Initiative or CITI). A private foundation (Advancing a Healthier Wisconsin) has just funded a large multi-year initiative by MCW IRB Chairs and senior regulatory staff, for the purpose of producing two different human research protections basic training tools designed for grassroots community organizations participating as partners in research. [Timeline: 3 years]

The CTSI will develop and present a series of repeating public interest programs on the layperson's (subject, participant, volunteer) role in health research with guidance from the Community Advisory Board (see Community Engagement). The programs will be presented in a variety of formats – e.g., live Science Café presentations, CTSI Radio Discovery. [Timeline: 2 years]

Goal 5. Improved inform consent processes. Beginning in January 2015, with state grant support, the MCW IRB will undertake a national survey of IRB translation policies for community organization partners and work with local community organizations to develop new, more flexible translation policies that satisfy the translation ascertainment needs of the IRB while offering simpler options to expand community participation in local health and social/behavioral science studies. A private foundation (Advancing a Healthier Wisconsin) has just funded one large multi-year initiatives by MCW IRB Chairs and senior regulatory staff, for this purpose.

Goal 6. Methods of collaborating with other CTSAs. The MCW IRB is a founding member of three consortia linking regional groups of CTSA institutions, and originator of the Master Reliance Agreement model for "centering" IRB oversight responsibility at one institution on behalf of all the collaborating institutions. These three consortia and their members are:

- the Wisconsin IRB Consortium [WIC]
    - MCW, University of Wisconsin Madison, Marshfield Clinic, and Aurora Health Care system
- the Midwest Area Research Consortium for Health [MARCH]
    - MCW, Indiana University, Mayo Clinic, The Ohio State University, University of Minnesota, and University of Wisconsin Madison
- the Greater Plains Consortium [GPC])
    - MCW, University of Kansas, Children's Mercy Hospital (Kansas City), University of Oklahoma, University of Texas Southwestern, University of Wisconsin Madison, University of Texas Health Sciences Center at San Antonio, University of Minnesota, and Marshfield Clinic

Within each consortium, members take turns assuming responsibility for IRB review on behalf of all member institutions. The net effect is that one IRB application and review will be effective for a half-dozen or more site implementations of a study. The MCW Master IRB Agreement model has been received favorably by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

The Southeast Wisconsin CTSI website provides central access for all eight CTSI institutions partners and "One City One IRB" partners to:

- a web-based application for a single coordinated IRB review effective for multiple engaged institutions, and
- a web-based display of summary information for IRB approvals applying to multiple engaged institutions (e.g., personnel by institution, study title and IRB number, IRB approval/expiration dates).

The MARCH and GPC consortia of CTSA institutions are completing their own websites providing central access for all consortia partners to:

- a web-based application for a single coordinated IRB review effective for multiple engaged institutions,
- a web-based display of summary information for IRB approvals applying to multiple engaged institutions (e.g., personnel by institution, study title and IRB number, IRB approval/expiration dates).

[Timeline: 3 years]

Metrics

Table 4: Regulatory Outcomes and Indicators

OUTCOME	INDICATORS/MEASURES	DATA SOURCES	RESPONSIBLE PERSONS	TIMEFRAME
Provide efficient, high-quality, and innovative regulatory services	"One City, One IRB" expansion to include collaborative (i) medical review studies and (ii) social/behavioral science studies -# & type of studies using One City One IRB # Other academic institutions and medical groups joining the alliance Time from IRB submission to approval, with or without assistance [3-5 year benchmark: *30% reduction in turn-around time for IRB submissions subject to full committee review & 40% reduction in turn-around time for IRB submissions subject to expedited review or exemption*] Investigator ratings on of service provided (IRB communication clarity, IRB efficiency, and IRB quality)	eBridge Waypoint REDCap	Regulatory Office IRB Navigator Evaluation	Quarterly, Annually
Provide easily accessible & efficient consultations	# of investigators served # of projects supported # of consult hours (per visit, per month, per quarter) Nature of consults & who provided them Efficiency of consults provided (time from request to consult provided (first meeting), reported by # of days) User satisfaction of service provided # of returning service requestors	Waypoint REDCap eBridge	Regulatory Office IRB Navigator Evaluation	Quarterly, Annually
Increase the number of educational opportunities available to those in SE Wisconsin	# of IRB members completing the CTSI Certificate # & type of community partners participating in MCW IRB's novel human subjects protection training curriculum for community partners [3-5 year benchmark: *at least 75% of local community engagement projects adopt training*] Knowledge and skills gained from IRB training and education [5 year benchmark: *at least 75% demonstrate skill/knowledge acquisition*] # of students completing CTSI's Responsible Integrity/Responsible Conduct of Research (describe students) # of investigators completing CTSI's Good Clinical Practice training course (describe investigators)	Waypoint	Regulatory Office CTO staff Evaluation	Quarterly, Annually
Promote innovative tools and methods to address barriers to clinical and translational research	# of IRB approved studies using consent documents translated into other languages commonly spoken by Milwaukee regional patients who don't speak English [3-5 year benchmark: *Increase by a factor of 4*]	eBridge	Regulatory Office	Quarterly, Annually

Table 4 outlines the primary outcomes, indicators, and data sources for the Regulatory Knowledge core. Waypoint©, CTSI's centralized database will serve as one of two primary methods in which process and outcome metrics are captured and collected across Regulatory programs and services. eBridge, the Medical College's regulatory database will be the primary source for data on efficiency (timing) and other information related to the nature of clinical and translational research happening across CTSI. Survey data (i.e., user satisfaction and quality ratings) will be gathered via REDCap. Key performance measures (benchmarks) are outlined in Table 5 utilizing baseline or historical data provided in Table 6, where available. Quarterly dashboards will be used to summarize key performance measures and outcome data by core component (i.e. Research Expertise and Methods). Dashboards and other evaluation reports will be shared with CTSI and

program leadership to aid in action, decisions and discussions related to continuous quality improvement and evaluation.

Table 5: IRB Approval Turnaround Time Goals /
In DAYS from submission to final documented approval

	Full Board Review	Expedited Review	
2015	75*	35	* Pilot year for one quick response IRB, with goal of 40 day review turnaround time
2016	62**	29	** Expand to two quick-response IRBs, with goal of 40 day review turnaround time
2017	52***	21	*** Maintain two quick-response IRBs, with goal of 35 day review turnaround time
2018	42****	14	**** Maintain two quick-response IRBs, with goal of 28 day review turnaround time
2019	35*****	10	***** Expand to three quick-response IRBs, with goal of 24 day review turnaround time

Table 6: New studies: Average days, submission to approval, by year

	2010	2011	2012	2013	2014	% Change (2010- 2014)
Full	62	61	56	75	79	+22%
Expedited	43	45	52	35	35	-23%

COMPONENT 5. RESEARCH IMPLEMENTATION AND PARTICIPATION.
LEAD: RACHEL SCHIFFMAN, RN, PHD
Module 5a: The CTSI Pilot Translational and Clinical Studies Program (PTC).
Leads: Ramona Tenorio, PhD and Reza Shaker, MD

Since 2010, our Hub PTC has leveraged NIH and Institutional funds to support 87 translational research awards totaling $3,777,942 with 297 investigators participating. As a result, these research teams have received more than $10 million in extramural funding (2.7:1 ROI); have published 40 manuscripts reporting their findings in diverse peer-reviewed journals. Some of these studies have generated key findings directly impacting diagnostics and patient management (See Overall Section).

Evidence suggests that larger, more diverse teams of researchers produce more high-impact research and novel ideas [1-4]. By their nature, the form and function of these teams helps diminish barriers between institutions and disciplines, while encouraging novel approaches to solving complex health-related problems and improving outcomes. An important requirement for our Pilot Grant Program in the past five years has been its multi-disciplinary component. This approach has been successful and has catalyzed the formation of a large number of multi and trans-disciplinary research teams of scientists. In this proposal, we will expand on this idea. Collaborating with the Community Engagement Module (CE) and using some of its mechanisms, we will engage and integrate the appropriate community of stakeholders and those impacted by health disparities across the life spectrum in identifying needs, developing concepts, forming teams and disseminating results (see Circle of Engagement, CE Module). In addition, we will collaborate with our clinical practice/health systems to Integrate Research Into Clinical Practice (IRICP) to facilitate and generate research ideas emanating from patient encounters in clinic. This approach provides us with the opportunity to encourage development of research proposals emanating from the clinic and, as important, from the community, to complement the traditional, investigator-inspired proposals. The overall goal of our PTC Module is to converge scientists and the community of stakeholders around topics of mutual interest to advance research along the translational continuum. In the following sections, we will first describe the 3 potential sources of proposal generation, followed by our funding mechanisms for our Pilot Pipeline.

Patient/clinic-inspired research proposals: This category of funding proposal is generated by clinicians and inspired by an important shortcoming observed in the course of patient care, such as, inadequate diagnostic modalities, therapeutics, or outcomes/ evidence based data, best practices, etc. We have tested this model for the past 2 years and have seen encouraging results, including the formation of 13 research teams and useable/ generalizable results (see Overview).

Community-inspired research proposals: These proposals are generated by a) clinicians and practitioners in our Community Based Research Networks (CBRN) and Practice Based Research Networks (PBRN), as well as community based health services, and b) by combined efforts of a community of stakeholders and our investigators through the Nucleating Workshop mechanism described in the community engagement module. The purpose of the Nucleating Workshops is to form community-informed research teams that will address critical issues in translational science. These groups will utilize workshop time to formulate a research proposal. These teams will continue to cultivate their proposal after the workshop leading to an application for CTSI Pilot funding (see Community Engagement Module-CE). The concept of pairing community and academic researchers has been tested in our institution (via the Advancing a Healthier Wisconsin Partnership Program-AHWPP). Learning from the experience of that program, we have tested and refined the Nucleating Workshop process with encouraging results of generating multidisciplinary research projects (we've had 11 of these workshops in 6 years). In the current proposal, the community of stakeholders, including community members, a community of patients, industry and patient advocacy organizations will be integrated further and play a crucial role in recognizing needs, developing concepts, supporting research and disseminating results through these Nucleating Workshops.

Laboratory/scientist inspired proposals: This is akin to traditional investigator initiated grants, which will cover the entire spectrum of translation from T1-T4. Whereas, the prior 2 mechanisms will be focused on T2-T4 and possibly T5. Proposals generated from each of these mechanisms will have the opportunity to access the funding paths described below.

Based on past awardees' feedback, we have learned that pilot funding may successfully generate promising data, but it may remain in need of additional data to be propelled into the next phase of translation. Therefore, the PTC Program, in this proposal has implemented a mechanism to remedy this shortcoming by devising the Pilot Funding Pipeline (Figure 1).

This pipeline is comprised of three Funding Paths, each with their own RFA release dates and review criteria but all using a streamlined, secure and flexible electronic application and review system; Research Electronic Data Capture (REDCap™). Linking the grant application process to REDCap™ allows for seamless evaluation and tracking. These Funding Paths need not be sequential, and investigators can enter the pipeline at any point. None of the NIH dollars will be used to support trials beyond Phase IIA, as mandated by NCATS.

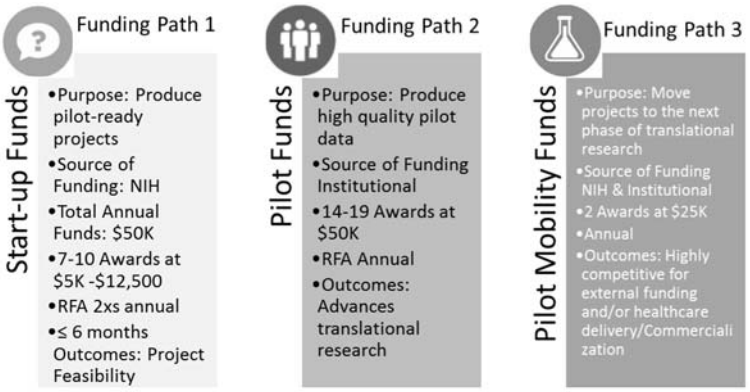


Figure 1 Pilot Pipeline

Funding Path 1: This path will fund pilot studies testing early stage hypotheses, which can provide data to develop projects that can progress along the translational continuum and promote solutions that would be applicable in multiple setting/conditions. $50,000 of the total PTC funds will be set aside to support a number of meritorious start up concepts. Depending on the merit and need of the submitted projects, we envision funding 7-10 short term (<12 months) projects across the translational continuum (ranging from $5,000 to $12,500 per project). Awardees will have the flexibility to determine and adapt evidence-based interventions in research design. Investigators will have the opportunity to utilize our Translational Research Innovation Acceleration Development (TRIAD) services (see NRO Component). Awardees will have to explain how they will utilize CTSI services and resources such as: the CTSI CTO for assistance with recruitment and trial design, Translational Research Units, and Bioinformatics I2B2 and REDCap™ services.

Award Solicitation and Review: An RFA for these funds will be disseminated twice a year via the CTSI website allowing for investigators to prepare for the annual CTSI Pilot Award (Funding Path 2). All applications will undergo an *In-Person Scientific Review*. The CTSI PTC will incorporate a broad spectrum of stakeholders: basic and clinical scientists, social scientists, patient advocates, community leaders, biostatistician, and Clinical Trials Officer as determined by the content of proposals in forming the Scientific Review Committee (SRC). The SRC will follow the NIH-style Review Criteria outlined in Table 1, as well as a PCORI model for scientific inclusivity (with in-person NIH-style review) to ensure the best qualified, and most promising clinical and translational science is funded. During feasibility project phase, researchers will be able to obtain full regulatory approvals for larger pilot projects. The outcomes of these studies must demonstrate a clear research path leading to a full pilot study proposal in order to be considered for funding at Funding Path 2. In the absence of progress (interim progress report at three months), funds will be frozen and/or rescinded per the recommendation of the PTC Committee the EC research portfolio management process.

Funding Path 2: Leveraging institutional funds, our hub will support 14-16 clinical and translational science pilot projects for one year at $50,000 each. These funds are intended to support projects across the translational continuum of T1 to T4 that are fully matured and have already proven feasibility and are ready to move to the next phase of research to collect important preliminary data which will lay the foundation for their long-term research goals by either applying for extramural funding or becoming ready to enter the IP/commercialization process.

Award Solicitation and Review: In 2013, the CTSI PTC Program developed a Two-Track RFA and Review Process (Translational Track 1, T1 to T2; and Translational Track 2, T3 to T4) to increase applications across the translational continuum and encourage multi-sector collaborations of basic scientists, clinicians, social scientists, community partners, government, and patients. An RFA will be disseminated annually on the CTSI website.

Applicants will first submit a mandatory 2-page Intent to Apply form, which will be reviewed by the PTC Committee for technical feasibility and compliance with RFA requirements, scientific integrity, and potential overlapping research. PIs of projects meeting these standards will be notified within 2 weeks via REDCap™ and receive a personalized link to submit the full application. The PTC Committee will identify appropriate peer-reviewers [4] based on the applicant pool.

Full Application: All applications must be sent through REDCap™ utilizing a standard format consisting of:

- Budget and budget justification, including supplies and personnel

- A six page description of the proposed research project including specific aims, background, and significance, how the project will incorporate special populations including women and minorities, relevance to translational research, research plan, future directions and literature citations.
- Project Schedule and Timeline
- NIH Biographical Sketch (PI and all key personnel; limit 4 pages per individual)
- Letters of Collaboration from each Co-Investigator to PI

Each application will be reviewed using a three-step process:

1. External Peer-Review: PTC will collaborate directly with CTSA member institutions in our MARCH and Great Plains Consortiums to generate a high quality, diverse, national reviewer pool, and to standardize pilot program evaluation metrics to include uniformity in report progress, performance, and quality improvement. Peer reviewers complete a detailed score sheet (Review Criteria in Figure 2) using the NIH Likert scale from 1 to 9. All scores will be tallied providing the average score and the standard deviation.

- Significance
- Innovation, Novel Technology and/or Novel Approach
- Approach and Feasibility
- Environment
- Translational Aspect
- Community Appropriateness and Engagement
- Team Science
- Overall scientific merit

Figure 2. Review Criteria

2. PTC Committee Review: will convene and review applications and scores, and any application with a large standard deviation will be flagged for Virtual Panel Mediation (VPM). VPM; an online virtual platform brings reviewers and a moderator together in an anonymous virtual setting to discuss the merits of an application. VPM will be open for one week; reviewers then are sent an email link survey to give their final Overall Impact Score and updated feedback. All applications and final score sheets will be sent to the In-Person Scientific Review Committee.

3. In-Person Scientific Review: All applications will undergo review by the SRC as described above (Path 1). Progress will be monitored regularly through quarterly reports. In the absence of progress funds will be frozen and/or rescinded per the recommendation of the PTC Committee and the EC research portfolio management process. Upon successful completion of these projects, if applying for extramural funding or entering commercialization process requires obtaining more data, these projects will be considered for Funding Path 3, to ensure momentum of translational impact.

Funding Path 3: Leveraging NIH dollars and institutional resources we will in meritorious cases provide further support to assist pilot projects towards external funding and/or commercialization as described above. 2 meritorious projects will be supported for an additional 1 year at $25,000 each.

Award Solicitation and Review: There is no RFA for this Funding Path, as applications are recommended after successfully completing previously funded projects.

Selection Process: Based on recommendation of the PTC Committee or request of the team leader, projects will be recommended to the EC for approval to undergo an in-person scientific review.

In-Person Scientific Review: All applications will undergo review by the SRC as described above in Funding Path 1, with the specific task to determine whether the project has high likelihood of acquiring the necessary data for applying for extramural funding and/or entering the commercialization process.

Comprehensive support for research teams: CTSI's Translational Research, Innovation, Acceleration and Development (TRIAD) and its Navigators will provide all investigators with one-on-one support on external funding opportunities and available supports and resources that may facilitate the advancement of research or preparation of research application.

Business and Cost Management: To augment NIH and Institutional funding in the next program cycle, the PTC Program will increase capacity and sustainability by leveraging funds from local philanthropic organizations and corporate sponsorships. NIH and other external funding will continue to be supplemented by MCW departments and central funds, and other institutional support.

Metrics: Evaluation is integral to CTSI program planning, implementation and structure, and occurs at two levels; internally and externally in collaboration with other national CTSAs as part of the NIH efforts to normalize CTSA policies, procedures, and evaluation metrics. Internal evaluation will continue to include "program model development, needs assessment, tracking and performance monitoring, continuous quality improvement, and process and implementation analysis" [5]. Table 1 outlines the primary outcomes, indicators,

and data sources for our PTC Module. Waypoint©, CTSI's centralized database will serve as the primary method in which process and outcome metrics are captured and collected. REDCap™ will be used to gather longitudinal data on awardee outcomes. Reports will be based on research benchmarks/timelines rather than quarters to ensure relevant information is captured at each stage of the research process allowing more effective program management leading to more reliable and valid data. Key performance measures (benchmarks) will be developed in year one of this proposal utilizing baseline or historical data, where available, to aid in achieving primary intended outcomes year to year. Quarterly dashboards will summarize key performance measures and outcome data by core component (i.e. Research Implementation and Participation). Dashboards and other evaluation reports will be shared with CTSI and program leadership to aid in action, decisions and discussions related to continuous quality improvement and evaluation. The PTC Program will focus on increasing the effectiveness of evaluation by adopting CTSA national standards and collaborating with other CTSAs to conduct regional program evaluations, as emulated in our MARCH consortium. The PTC Program will increase our outreach to Wisconsin and the region to disseminate knowledge about CTSI. Successful projects and significant findings will be spotlighted in an annual PTC Brief.

Table 1: Pilot Translational and Clinical Outcomes and Indicators

OUTCOME	INDICATORS AND MEASURES	DATA SOURCES	RESPONSIBLE PERSONS	TIME FRAME
Contribute to an increase in collaborations across departments, institutions, disciplines, industries, and CTSA hubs	# of multi-disciplinary collaborations; # of institutions involved; # and type of hub collaborations (MARCH, etc.); Nature of collaborations stimulated (research vs program, etc.) and results (translational solutions developed, program best practices, etc.); # of awards incorporating special populations	Waypoint REDCap™ reports	PTC and Evaluation	Quarterly and Annually
Improve the availability of funding for CT research and strengthen and expand the quality and capacity for clinical and translational research	# of applications by year and funding pipeline phase; # of awards, $ funding amount, rating of methodological quality of trial design; # of awards falling on T1-T4 continuum; # and type of awards advancing through funding pipeline (Time it takes-efficient process?, support required -time, resources, etc.); # of vouchers used and for what services; Time from Notice of Grant Award (NOGA) to Date of First Accrual (FA); Study Start-up time: Time in days from date of IRB approval to first subject accrual; Studies with adequate accrual- recruitment; Length of time spent in recruitment	Waypoint REDCap™ reports Application review forms	PTC and Evaluation	Quarterly and Annually
Foster the identification and development of best practices and scholarship in Clinical and Translational Research	# and type of roadblocks identified for the success of clinical translational research; # and type of solutions implemented		PTC and Evaluation	Quarterly and Annually
Contribute to the increase in CT research to clinical practice (T1,T2) and to our community (T3-T4) [improve clinical practice]	# and type of presentations; # and type of publications; # and type of funding applied for and received; # of awards falling on T1-T4 continuum; # and type of successful feasibility outcomes identified; Nature of translational roadblocks identified/researched through PTC awards; # and type of awards advancing through funding pipeline- # and type advancing to path 3 & 4; Resulting research outcome; New discoveries; Policies changed; FDA-approved drugs; Technology transfer products	Waypoint Applications REDCap™ reports	PTC and Evaluation	Quarterly and Annually

<u>Module 5b: Integrating Special Populations.</u> Leads: Dawn Bragg, PhD and Calvin Williams, MD, PhD

Introduction and Rationale. CTSI is uniquely situated to serve underrepresented populations, children, aged and veterans. The overall makeup of our region is 14% African American, 9% Hispanic/Latino, 1% Native American, and 3% Asian [6]. Wisconsin also is home to the third largest Hmong community in the United States [8], boasts 11 federally recognized Native American tribes, and has seen the population of our vibrant Latino community increase by 74 percent between 2000 and 2010 [7]. Our investigators have worked with these communities on various projects, including sickle cell disease and hypertension studies (African-Americans), diabetes (Hispanics), Alzheimer's disease (older adults) and the HIV community. 2011 participant ethnic/racial data indicates that 9.2% were Hispanic/Latino, 0.4% American Indian, 1.7% Asian, and 25.4% African American, numbers that have been fairly steady. 51.5% of all our research participants were female.

In the next five years, we will introduce systematic efforts to leverage the tremendous diversity of our underserved and special populations, such as the elderly, children and our veterans in collaboration with our CE module. This includes engagements with Milwaukee community organizations, such as the Gerald Ignace Indian Health Center. Interactions with these special populations have been enhanced by acknowledging their legitimate apprehension of working with the medical community and collaborating with community members to set standards of accountability and responsibility in research. CTSA 1.0 provided the resources to initiate this undertaking with the development of the Regional Community Engagement model (RCE, see Section 3c) and

establishment of the Community TRU (C-TRU), which brought CTSI investigators and nursing staff closer to groups that rarely venture from their communities. CTSA 2.0 outreach efforts will be aided significantly by the creation of the new CTO and the establishment of new TRUs at MU and UWM, bringing CTSI investigators and nursing staff in closer proximity to populations that differ from those seen at the hospital-based TRUs and reaching out to groups of potential participants with different special needs.

Connecting to Special Populations. Our recruitment paradigm, which supposes that every patient is a potential research participant, has focused heavily on connecting with patients seen at the clinics adjacent to our TRUs. This effort has been useful, to a point. For example, of the 190 studies currently active in the TRUs, 103 serve special populations**,** including 47 of the 89 pediatric studies currently active at the Ped-TRU. Of the 14 active studies being carried out at the VA-TRU, 11 focus on such issues germane to our geriatric population, like Alzheimer's disease and orthopedic medicine. Several of our largest research programs span multiple groups (Table 2). Among these are studies in sickle cell disease (SCD), von Willebrand disease (vWD), cystic fibrosis, and phenylketonuria (PKU). Our partners at MU also are performing research studies with PKU, while investigators at MU and UWM are investigating autism**.** The C-TRU (Section 5c) has cut its teeth on several projects that have taken A-TRU nurses into local clinics and non-governmental organization facilities, expanding our population base to Latino and Native American groups around the area. Described below are several current research efforts that focus on special groups (either ethnic/racial populations or specific diseases) and exemplify the way investigators utilize patient organizations and advocacy groups in research recruitment and development. We will maintain and enhance integration of special populations through 3 goals.

Table 2. Anticipated Enrollment of Special Populations in Current TRU Protocols

Population:	Studies	Planned Participants	Sites
Sickle cell disease	15	951	FH,CHW
Bleeding disorders	9	689	CHW,BCW
Alzheimer's disease	10	2529	FH,ZVAMC
Cystic fibrosis	10	807	FH,CHW
Resuscitation Res.	9	692	FH,CHW
Phenylketonuria	6	121	CHW

Goal 1. Special Populations Served through the Hospital- and Community-based TRUs

▪The Adult Sickle Cell Disease (SCD) program, in collaboration with investigators from the BCW Blood Research Institute and CHW integrate clinical research into routine clinical care, providing every patient with the opportunity to participate in research studies that the CTSI has been supporting through nursing and infrastructure, along with Bioinformatics and Biostatistical support. The Adult SCD program, which complements a large pediatric SCD program at the CHW CRI, leads in the accrual of the 10-site, phase II study of the adenosine A_{2A} receptor agonist, regadenoson.

▪CHW and CRI offer programs that engage the community and its special populations, like the Community Health Improvement for Milwaukee's Children (CHIMC), a community-based participatory research initiative established to address immunization disparities in Milwaukee's low-income children; the Center for Clinical Effectiveness Research, whose purpose is to generate, evaluate, and synthesize research findings that will lead to the best and safest care for children, across the continuum of care environments; the Family-Centered Delivery of Motivational Interviewing (MI) to Enhance Type 1 Diabetes Self-Management (PCORI), which aims to assess the impact of family-centered delivery of MI; and Project Ujima, which provides victim services to youth injured through interpersonal violence and families of adult homicide victims. In addition to these programs, the CRI sponsors several major research initiatives, including:

▪The Immune Deficiency Program (IDP) in the Dept. of Pediatrics focuses on defining and treating genetic defects that affect the immune system and also oversees the Wisconsin Newborn Screening Program for Severe Combined Immunodeficiency (SCID). The IDP program has developed novel treatment strategies for complications of primary immunodeficiencies. Over the past 5 years, the IDP has identified 15 patients with SCID, leading to the initiation of statewide newborn screening program for SCID. Evaluating these patients may lead to the discovery of new genetic disorders that will ultimately benefit children affected with these disorders, in addition to providing valuable knowledge of the human immune system.

▪The adult and child Cystic Fibrosis (CF) Program has existed at MCW and CHW for more than 20 and 30 years respectively and provides a unique opportunity to treat patients as they progress through the lifespan and offers consistent research benefits. The Pediatric CF Clinic at CHW currently treats more than 200 CF patients. The CF Center is home to a well-known outcomes study that demonstrated improved clinical outcomes through early intervention and in recent years has been involved in several other large multicenter studies. A basic research component focuses on candidate gene analysis and phenotype-genotype

correlations in CF. The pediatric CF investigators work closely with those who study the disease in adults. Indeed several studies are currently underway simultaneously in both populations.

- Infantile Hemangioma and PHACE. Parents of patients with Infantile Hemangioma and PHACE use connected technology (social media) networks to find and connect to other parents to compare their experiences with health care providers, symptoms, and pharmacologic intervention. This new information exchange phenomenon should increasingly influence families/patients to seek therapy and/or enter clinical trials. Translational researchers increasingly use the Internet to recruit, communicate with participants, and even collect data. Patient advocacy groups have successfully mobilized their members to study the effectiveness of investigational treatments. Existing websites can be expanded to include information about specific hemangioma projects and facilitate direct patient recruitment.

The largest population of US veterans are age 65-69, a group that ideally benefits from and can contribute to research studies such as Alzheimer 's disease, conducted at our partner institutions, Froedtert Hospital or the Zablocki VA Medical Center (ZVAMC), a rich source of potential participants. One recent clinical trial of gout and cardiovascular disease using the VA-TRU involved soliciting patients from the VA outpatient clinics regardless of age, resulting in a cohort recruited with an average age of 80. Another group has successfully enrolled patients from the outpatient geriatrics clinics to study shoulder pain in an elderly population. A very successful annual Research Day at the VA advertises clinical trial participation and highlights available trials. Recruitment also has occurred via fliers placed in relevant clinics and in and around the TRU. The Million Veteran's Program boasts one of the highest rates of enrollment in the country; about 1000 participants have been enrolled in this program which is supported by our VA-TRU. Once these patients are enrolled, a TRU bulletin board advertises other volunteer opportunities. Recruitment efforts will be aided by the CTO (Module 6a) and advertising in the various databases described in Section 6b, as well as Veterans organization newsletters and a website under development. Additionally, we plan to continue our close collaboration with the MCW Division of Geriatrics of the Department of Medicine. The CTO recently hired a full-time clinical research coordinator with marketing experience and special expertise in geriatrics to be stationed at the VA-TRU. This will allow us to extend research expertise and assistance to the VA investigators. We are exploring the possibility of adding a link (recognizing the complexities involved)to the Veterans' EHR connection "MyHealtheVet" module that is accessed by the patients to access their heath record (MyChart equivalent of EPIC) to our CTO`s clinical trials site (FACT, ResearchMatch) to enhance our engagement of veterans with translational research.

Goal 2. Connecting to Special Populations through TRUs at our Partner Institutions. The new TRUs at our partner institutions provide opportunities to recruit from segments of the local population who live further afield and who have frequently been underrepresented in research efforts at the hospital-based TRUs. The local Hispanic community, which represents a large and rapidly growing segment of the local population, is situated nearby MU. The following highlights areas where our partner institutions are able to recruit from some of these special populations and how the CTSI has strategically partnered with these institutions.

MU and MSOE: Orthopedic Medicine in Children**.** MU's Orthopaedic & Rehabilitation Engineering Center promotes and encourages significant advances in clinical research, building upon prior successful collaborations in the fields of orthopaedic biomechanics, biomaterials, rehabilitation engineering, and human motion analysis. A novel quantitative model was developed for the evaluation of upper extremity dynamics in children with spina bifida. This model, being used to study forearm, crutch-assisted walking patterns, has potential for improving clinical intervention strategies, therapeutic planning, crutch design, and quality of life in children. Control of standing posture is a challenging task for children with cerebral palsy. This group developed a bi-planar model of postural stability that may help to understand the underlying factors affecting instability and ultimately lead to better treatments. The MSOE Rapid Prototyping Laboratory works closely with investigators at MU. Rapid prototyping starts the design of a prosthetic or orthotic device with the specific patient's anatomy. A patient's specific alignment characteristics are included in the prototype design, allowing a better customized fit. Through this process, the number of times that a prosthetic/orthotic has to be refitted is decreased, thus cutting down on overall cost.

Among other initiatives and studies at MU, 4 studies focus on the Hispanic community, including women and children (600 participants); 3 emphasize geriatric populations (236 participants, plus a fourth involving 350 veterans from the ZVAMC); a national study that will study 20,000 homeless veterans; 3 involve children and adults with autism (1120 participants); 3 additional studies on children (2750 participants); and 4 additional

women's studies involving 465 volunteers. The establishment of a MU-TRU will allow us to provide additional infrastructure and nursing support to benefit the translational science currently under investigation at these sites.

UWM: Pediatric Neurodevelopment**.** UWM's Child Neurodevelopment Research Laboratory studies aspects of child development in children with developmental disabilities, including cognitive, behavioral, and emotional functioning, with the goal of better understanding the relationship between genes, brain function, and behavior. Many children with genetically-based developmental disabilities (e.g. Williams Syndrome, Neurofibromatosis-1, and Autism Spectrum Disorders) are included in the studies. The Child Language Lab supports research focusing on child language development, impairment, assessment and intervention. The lab currently is focusing on emergent literacy and early language acquisition, the communicative behaviors of teachers and childcare providers during interactions with young children, and the development of an integrated database system for young children with disabilities.

The development and anticipated expansion of the C-TRU now enables us to tap clinics that serve individuals who represent potential research participants and help investigators conduct their research studies in the neighborhoods where these patients reside. Establishing new TRUs at the locations of our community partners (Module 5c) will extend our reach to new segments of the local population, even into the suburbs.

Goal 3. CTSI Pilot Program Support for Inclusion of Special Populations. This program has and will continue to nurture the development of investigators whose research efforts involve the study of special populations. Diversity will be used as one yardstick in evaluating pilot projects for funding (see Module 5a PTC). We will orient these investigators to the functions of the CTSI and provide resources to enable them to carry out their research goals, including but not limited to IRB support, TRIAD, the CTO, and the C-TRU.

Metrics.
Table 3 outlines the primary outcomes, indicators, and data sources for ISP. Waypoint©, CTSI's centralized database will serve as the primary method in which process and outcome metrics are captured and collected. Through the TRUs, data will continue to be captured via the TRU database and integrated through web services technology. Key performance measures (benchmarks) for the program will be developed in year one of this proposal utilizing baseline or historical data as available, to aid in achieving primary intended outcomes year to year. Quarterly dashboards will be used to summarize key performance measures and outcome data by core component (i.e. Research Implementation and Participation), and will be shared with CTSI and program leadership to aid in decisions regarding continuous quality improvement and evaluation.

Table 3: Integrating Special Populations Outcomes and Indicators

OUTCOME	INDICATORS AND MEASURES	DATA SOURCES	RESPONSIBLE PERSONS	TIME FRAME
Increase engagement of specialized populations through the Hospital-based TRUs.	# and type of studies engaging special populations, by TRU site (FH, CHW, ZVAMC) and CTO # of planned participants vs # participating Type of special populations [5 year benchmark: *increase studies focusing on older adults by 25%*] # of pilot awards focusing on special populations	Waypoint and TRU database	Participant & Clinical Interactions; Evaluation	Quarterly and Annually
Increase engagement of specialized populations through CTSI partner institutions and the Community TRU.	# and type of studies utilizing CTRU # of planned participants vs # participating Type of special populations # and type of studies at MUTRU # of planned participants vs # participating Type of special populations	Waypoint and TRU database	Participant & Clinical Interactions; Evaluation	Quarterly and Annually

Table 4: Proportion of clinical and translational research projects that incorporate minority and health disparity populations	
Population:	**# of studies:**
Blacks/African Americans	12/1807
Hispanic/Latinos	8/1807
American Indians/Alaskan Natives	0/1807
Asian Americans	3/1807
Native Hawaiians & other Pacific Islanders	0/1807
Socioeconomically Disadvantaged Populations	3/1807
Rural Populations	5/1807
Other (site defined)	
Veterans	3/1807
Planned Emergency Research	12/1807
AIDS-Intervention Research (CAIR)	25/1807

Our IRB does not systematically track these data, therefore we used study titles to discern study population for the purpose of the FOA. In actuality, we estimate these numbers are likely higher, especially if reached through studies targeting the general population.

Module 5c: Participant and Clinical Interactions (PCI). **Lead: Ryan Spellecy, PhD**

Our CTSA hub is committed to the highest quality research possible. We have devised three goals to achieve this objective. This program will work closely with the Efficiency and Quality Module, which will use LEAN processes for improving the efficiency of our research infrastructure. In addition, this current module will benefit from the close collaboration between Regulatory Knowledge and Support as well as the Clinical Trial Office leaderships. Our goals are:

Goal 1. Actively promote quality.
Goal 2. Vigorously pursue efficiency.
Goal 3. Ensure compliance with federal regulations regarding registration of clinical trial.

Goal 1. We will actively promote the highest quality of human subjects research, screen actively for scientific or ethical flaws, bar implementation of flawed studies, and use identified flaws as a timely educational/training opportunity for the entire investigator community.

(1a) To promote the highest quality of human subjects research, we will require that the Principal Investigator, co-investigators, and study coordinator for every clinical or translational study complete the following training courses on a three-year renewable basis with the following content. See Course Table 5.

The content of all these courses will be integrated and presented as a single, day-long course ("Boot Camp for Clinical Investigators") by faculty and compliance specialists with the appropriate expertise. In addition, two CTSI hub consultation services will be available to every study team for planning as needed/requested, including: Biostatistics/Epidemiology Research Design (BERD) program Consultation Service, and the Bioethics and Medical Humanities Center Consultation Service.

Course Table 5
Human Subjects Research Protections
FDA/ICH Good Clinical Practice
Financial Conflict of Interest
ClinicalTrials.gov policy
Responsible Conduct of Research
NIH Grants Policy, as applicable

(1b) To effectively identify and remediate studies posing either scientific or ethical flaws, we will implement the following mechanisms and procedures:

- Every human subjects research study will be reviewed by a formal Divisional or Departmental (i.e., with expertise) Scientific Review Committee before the study can be submitted for IRB review. This scientific review will be documented for the IRB, and scientific approval is a necessary precondition for the initiation of IRB review. All cancer trials will undergo additional scientific review via the Cancer Center Scientific Review Committees.
- For every greater-than-minimal-risk human subjects research study, all IRB members will receive the IRB application and all supporting materials (including protocol, Investigator's Brochure, correspondence, and technical materials) at least ten days before the scheduled IRB review meeting, to ensure that all members have adequate time to study the application, pose questions, consult reference material and/or request expert consultation for the IRB, and generally prepare.
- For every greater-than-minimal-risk human subjects research study, all new study applications are assigned to two IRB members for exhaustive in-depth "lead" review to guide the Committee discussion.

The IRB will disapprove studies in situations where investigators are not willing to discuss or address regulatory questions or ethical flaws identified by the IRB review process, after being given opportunities in writing to discuss the problems, meet with the IRB Chair and/or the Convened IRB, and pose alternative solutions.

(1c) To ensure that there is a process for individual investigators and the institution to learn from identified scientific and/or ethical flaws in human subjects research and to capitalize on identified flaws as timely education/training tools, the following mechanisms and procedures will be implemented:

- The CTSI Clinical Trials Office Director will collect written documentation of scientific flaws identified by the Scientific Review Committees and the Biostatistics/Epidemiology Research Design (BERD) program Consultation Service on a quarterly basis.
- The Human Research Protections Program Director will collect written documentation of ethical flaws identified by the IRB and the Bioethics and Medical Humanities center Consultation Service on a quarterly basis.
- Semi-annually, the two Directors will meet to review the problems and flaws documented in the last six months and identify those flaws that recur most often and those that have the greatest teaching value. Collaboratively, the two Directors will draft scientific flaw/ethical flaw lessons from the bi-annual records and assign qualified teachers for each lesson, and organize these teaching materials into a regularly scheduled, centrally located semi-annual CTSI Grand Rounds on "Flawed Human Subjects Research" Selected summary of the grand rounds will be posted on the CTSA portal/CTO website for extended distribution.

Goal 2. We will vigorously pursue efficiency by overseeing and centrally monitoring the planning and conduct of studies—i.e., appropriate study design, realistic recruitment goals, realization of enrollment, follow-up success, timely submission of data, rigorous data quality monitoring throughout each study, orderly closeout, and timely publication of results.

(2a) To centralize oversight and monitoring, all clinical studies will be registered from Day 1 of planning with the CTSI Clinical Trial Office. The progress of each project to implementation and completion (or, to withdrawal) will be recorded in uniform steps using CTO Workflow Forms by a single new position/role – the Clinical/Translational Studies Performance Monitor – within the CTO.

(2b) To monitor and analyze the progress of each clinical study toward its stated goals, the Clinical/Translational Studies Performance Monitor will compare recruitment goals, follow-up rate goals, planned data transfer milestones, closeout goal dates, and publication goal dates with actual results. The Monitor will also collect documentation of all data quality monitoring reports and audits from all sources to characterize and rank-order the data quality success rates of each study team. The Monitor will issue quarterly study performance reports for investigators, the CTO Director, CTSA Director, and the Senior Associate Dean for Research.

The quarterly performance reports will highlight under-performing studies; under-performing studies will be put on notice for no more than two quarters before being asked to show cause why they should not be administratively terminated. Studies that do not closeout in an orderly fashion, analyze results, or do not publish results in a timely fashion will be put on notice for no more than two quarters before the investigators will be earmarked as under-performing or unproductive investigators.

Investigators whose studies have been terminated administratively for reasons of under-performance and those who have failed to analyze results or disseminating findings in a timely fashion will not be eligible for further CTO support, except under the conditions of a formal supervised corrective action trial.

Goal 3. We will <u>ensure compliance with federal regulations</u> regarding registration of clinical trial. Our hub already has a centralized mechanism and procedures in place for ensuring that all "applicable clinical trials" are registered and post their results in clinicaltrials.gov, as required by the Federal Drug Administration Amendment Act (FDAAA). In this proposal, we will expand this initiative to require the registration of all clinical studies and trials in clinicaltrials.gov, and to systematically train clinical investigators for proper registration and reporting.

(3a) Currently “applicable studies” that are required to register and post their results in clinicaltrials.gov are routinely identified at the time of IRB submission by deployment of specific screening questions and by active checklist-guided screening IRB office staff; those studies determined to be definite or possible “applicable trials” are promptly flagged for the investigators and for the lead clinicaltrials.gov consultant/trainer, who follows through to ascertain registration. In this proposal we will expand this requirement to apply to all studies.

(3b) The CTO will offer monthly classes on the procedures for registering and reporting results in clinicaltrials.gov for the entire CTSA hub community. CTO also will maintain “how-to manuals” on reporting and results on the CTSI website; offer individual study-specific consultations and assistance on registration/reporting; and be available to field any questions that arise.

Metrics

Table 6. Number of IRB Protocols Approved by Institution

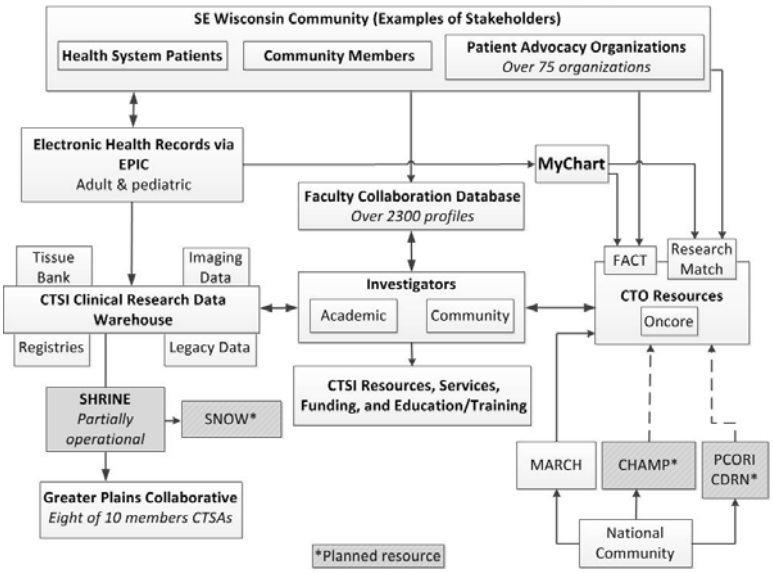
OUTCOME	INDICATORS AND MEASURES	DATA SOURCES	RESPONSIBLE PERSONS	TIMEFRAME
Ensure that high quality human subjects research is conducted	# and type of training opportunities offered; # of participants by training program/resources (CITI, GCP, Ethics, CTO IRB Boot camp, etc.); # of adverse events (AE) reported to MCW IRB; # of studies meeting accrual goals (TRU, CTO studies only); # of studies requiring a DSMB # of studies utilizing CTSI’s Research Subject Advocate # of studies registering/compliant with clinicaltrials.gov	Waypoint eBridge	PCI, CTO, Evaluation	Quarterly and Annually
Aid and facilitate effective and efficient clinical translational research	# of studies/investigators using IRB navigator support and pre-review services; # of Study Start-up time: Time in days from date of IRB approval to first subject accrual Studies with adequate accrual (recruitment); Length of time spent in recruitment; # of successfully completed projected enrollment for a given calendar year; # of and qualitative data on successfully completed follow-up goals (by follow-up interval) for a given calendar year; # of successfully met projected data submission milestones for a given calendar year; # of successfully closed out their study site on schedule for a given calendar year; # of successfully published or otherwise disseminated results within a reasonable period, for a given calendar year evidenced important data quality problems for a given calendar year; Success rate of registering “applicable trials” before enrollment of first subject, for a given calendar year; Success rate of reporting results for “applicable trials” on schedule, for a given calendar year; Success rate of registering other (non-applicable) clinical studies and trials before enrollment of first subject, for a given calendar year; Success rate of reporting results for other (non-applicable) clinical studies and trials, for a given calendar year; Investigator satisfaction with clinicaltrials.gov training and support, for a given calendar year (annual survey)	Waypoint eBridge	PCI, CTO, Evaluation	Quarterly and Annually
Vigilance for scientific or ethical flaws, and use of examples for educational purposes	# of and specifics of scientific flaws flagged by the Scientific Review Committees; # of scientific/ethical flaws framed as teaching examples for the investigator community; and number of investigators involved in the review of each example flaw; # of and specifics of scientific ethical flaws flagged by the IRB or any other administrative body; # of number/specifics of each study application disapproved by the IRB; # of all major protocol violations (i.e., serious and/or continuing non-compliance) reported to the IRB			Quarterly and Annually

COMPONENT 6. NETWORK RESOURCES AND OPTIONAL MODULE. LEAD: TOM AUFDERHEIDE, MD

I. Module 6a. Multisite Study Support. Lead: Amit Gode, MD, MPH and Gilbert White, MD, PhD

Goal 1: Establish a local centralized study support unit (SU) to facilitate implementation of multisite studies and serve as a liaison to the planned CTSA-support centers (CT-SC). In 2014, in collaboration with the MCW Cancer Center and the Blood Center of Wisconsin, our CTSA hub developed and operationalized a regional Clinical Trial Office (CTO) on the MCW platform with the ability to offer services to all hub partners. This CTO offers a comprehensive array of services and supports, such as support and recruitment units (SU and RU) making it to be an ideal vehicle to connect and collaborate with NCAT's planned CT-SCs and CT-RCs. The CTO capabilities and services are fully integrated into our Biomedical Informatics Connectome (BIC) (figure 1) providing an unprecedented connectivity between data warehouses, investigators, community of stakeholders and CTSI services. As shown, our data warehouse is connected to the CTO and provides investigators with the mechanism to search de-identified data for patient cohorts. An e-consent with honest broker mechanism is included to allow data identification and contact following IRB approval (see biomedical informatics module). Important first steps have been taken to enable the efficient planning and implementation of high-quality multi-center research that will harmonize standards and best practices and will promote the conduct of clinical trials in a methodologically sound, compliant, scalable, expedient, and cost-effective manner. This unit works closely with MARCH (Midwest Area Research Consortium for Health) in all aspects of our multi-CTSA trials. The CTO's various units will facilitate start-up and implementation and serve as our liaison to the planned CTSA support centers (CT-SCs). We have created the position of Participant Recruitment Facilitator (PRF) to support this initiative (see budget). As part of BIC, we have established a website for all CTO-related services that makes it easy for investigators to request services and afford participants the opportunity to be informed of and enroll in available trials. The CTO encompasses 8 distinct components that render it ideal to function as a local study support and recruitment unit. Here, we briefly discuss the CTO services that will facilitate the conduct of multisite trials and studies.

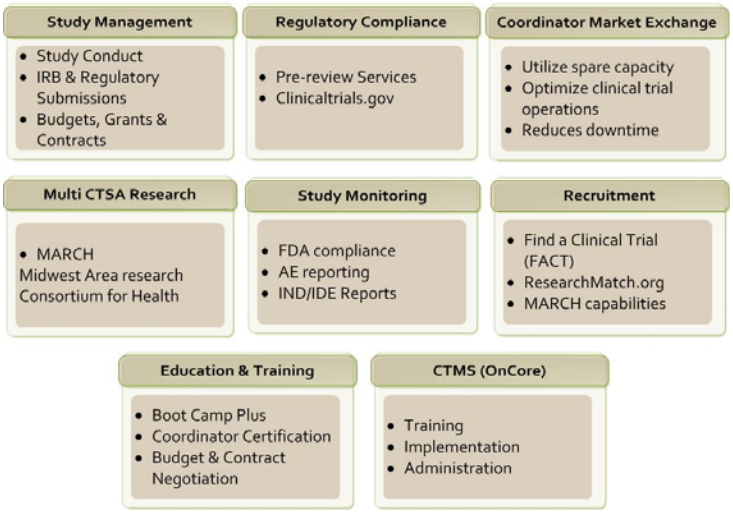
Figure 1 Biomedical Informatics Connectome (BIC)



Study Management. The CTO will comprehensively cover all aspects of study conduct, including regulatory documentation support and IRB submissions. Trained research coordinators will prepare and negotiate budgets, manage grants and contracts, facilitate site initiation visits, monitor visits, and prepare timely AR reports. The CTO will implement checklists, SOPs, and templates for fulfilling IRB, OCRICC, and other organizational compliance requirements. The Study Management service will be billed back as fee-for-service, and we aim to operate as cost-neutral during the next year of operation. All chargeable services provided through the CTO will have a transparent cost structure and the same cost mechanism will work across partner institutions.

Regulatory Compliance. Complementing CTSI services, the CTO will provide investigators with IRB pre-review services that include a comprehensive review of all drafts to assure the accuracy and consistency of all study documents, and protocol review providing analysis of recruitment procedures, data collection, risks,

Figure 2. Regional Clinical Trials Office Services



safety precautions, and protection of confidentiality in order to facilitate the submission of complete, accurate, and thorough applications to the IRB. The CTO will act as a central clearing house for fulfilling registration requirements at *clinicaltrials.gov* for applicable clinical trials. Quality Assurance will initially consist of an Educator/Monitor to ensure that the PIs and CTO staff adhere to all research regulations and enhance the quality control functions for all clinical trials. The CTO Monitor will conduct formal seminars and workshops for clinical trial staff and investigators on all aspects of clinical research management and trial conduct. GCP training modules and training, in accordance with the expected new guidance from NCATS, will be held as often as needed and will be made mandatory.

Coordinator Market Exchange. Funding and time availability in clinical trials is often unpredictable and sometimes leads to temporary over- or under-utilization of staff. In instances when the CTO cannot fill this gap, we propose to create an open exchange, where investigators share their resources. The CTO will act as an honest broker to fill gaps in research support. The market exchange concept is an easy means in which to maximize established resources and enable departments to either borrow or lend out their excess capacity.

Study Monitoring. Monitoring of FDA-regulated investigator-initiated trials (IITs) is standard practice to industry and cooperative group trials. Currently, our hub has no centralized resource to monitor ongoing research trials, forcing departments to hire expensive external monitors. The number of IITs on campus is expected to increase to at least one-third of all trials. The Monitoring Center will be a new service housed in the CTO and provided as fee-for-service.

Recruitment Unit/ Services. The CTO has hired a database manager who acts as a central repository for all inquiries from patients and PIs, and those from industry. The TRUs at these sites, along with those at the Cancer Center, Marquette, and ultimately UWM will all be key to this effort. In addition, this portal offers the potential for eventual expansion to other local institutions. In addition, the new CTSI Translational Research Innovation Acceleration Development (TRIAD) system will be instrumental in linking these diverse mechanisms to the CTO. TRIAD will improve efficiency, guide investigators who wish to study specialized populations to community resources, and then assist with their efforts to navigate the processes necessary to initiate studies through the CTSI and their respective organizations. Finally, our participation in MARCH will help provide potential participants access to trials at other well-known academic medical centers and CTSA hubs, while offering us a larger catchment area in which to recruit study participants.

Education and Training. The Office of Research at MCW in collaboration with the CTSI currently offers a 'Boot Camp' training program for research coordinators, which CTO plans to revamp and offer over two days several times during the year, ultimately providing certification to participants. The CTO also will create a targeted training module suitable for investigators. It is expected that training new personnel will shorten time spent on preparing IRB submissions of improved quality. The CTO also will work with the Offices of Compliance at MCW and its partners to initiate a coverage analysis process to recoup research-related professional fees for the Institution.

Clinical Trial Management Software (CTMS). To support our clinical trials efforts, MCW has purchased OnCore, a CTMS software that interfaces with EPIC to allow investigators to enter all study-related data in a comprehensive and systematic fashion. This web-based system provides users secure access from any location to record, manage, and report on data associated with the operation of clinical trials. OnCore is a powerful tool to strengthen research infrastructure and optimize study management processes and workflows. The system can then run custom reports, from enrollment targets to financial information, and generate data for recruitment rates, retention rates, study cost performance indices and other tools to help Investigators focus resources towards optimal management of their trials. Budgets and coverage analysis can be managed through this system, which also strengthens compliance by tracking regulatory approvals. We hope to customize the software for OCRICC submissions and link to the IRB's electronic submission for reporting of adverse events as well. By providing access to this system, the entire research enterprise can be streamlined. The CTO has hired an OnCore program manager to train study coordinators across campus and help to build study calendars into the system. By making OnCore available to all of the CTSI partner Institutions, we foster more efficient networking. Multi-institutional Study Conduct Support is described below.

Goal 2. Strengthen the existing regional Community-based Research Network (CBRN) in preparation for participation in multisite studies. In pursuit of engaging in cross-CTSA collaborations, MCW and five other CTSA sites (Indiana University, Mayo Clinic, Ohio State University, University of Minnesota and University of Wisconsin-Madison) were united in 2012 when they founded the Midwest Area Research Consortium for Health (MARCH). MARCH is one of the first true CT-SCs aimed at streamlining research resources across CTSAs. MARCH will assist investigators with both federally-funded and industry-based

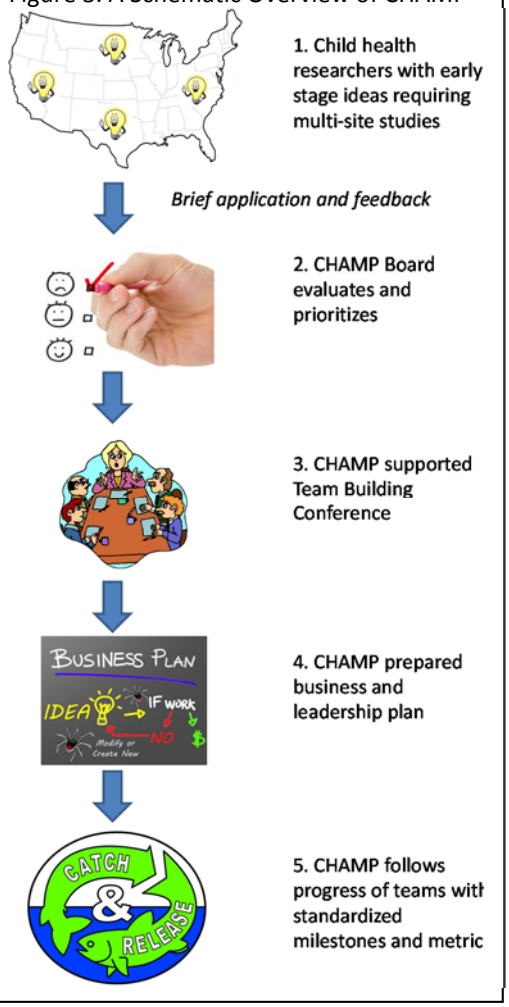
research to provide centralized trial management resources. The consortium allows effortless conduct of clinical trials at all or any of the 6 sites through a single IRB approval, one contract, and one master budget. Additionally, MARCH will assist investigators with biostatistics support, study monitoring services, and establishing DSMBs. Taking a cue from the Greater Plains Consortium, MARCH is now working to establish a similar data sharing agreement between its members, to be finalized in spring 2015. MARCH has been successful in establishing collaborations with industry leaders such as Novo Nordisk, Eli Lilly and local Wisconsin pharmaceutical companies. MARCH CTSAs are now their "preferred sites" for new trials. The central coordination center (in the manner of a CRO for industry studies) will help maintain compliance, sustained recruitment rate, patient safety, and centralized budgets. Through the coordination center, we also plan to extend the CTO study monitoring function to other MARCH sites. The MARCH consortium also will be utilized for developing shared education resources via the new Translational Training/Educational Collaboratory (TTEC) program. Our local study support center - the CTO - acts as a liaison between MARCH and our hub.

The Great Plains Collaborative (GPC), part of the Patient-Centered Clinical Research Network (PCORnet) Clinical Data Research Networks (CDRN): Improving Infrastructure for Conducting Patient-Centered Outcomes Research (PCOR). As described in bioinformatics, GPC links 10 medical centers in 7 Midwestern states to exponentially increase the number of de-identified patient records accessible to collaborative members. The "One City One IRB Alliance" as well as our Master Reliance Agreement with UW-Madison CTSA, Marshfield clinic and the Great Plain Cooperative will facilitate and regulatory processes

Finally, the CTSI is joining with 18 other CTSA Hubs in establishing the Child Health Research through Multisite Planning (CHAMP). CHAMP is a novel approach to support investigator-initiated, multi-site studies broadly focused on child health research. The CHAMP concept was selected for presentation at the July 2014 CTSA Principal Investigators meeting. The idea has been vetted by a group of nationally recognized leaders in child health research. Drs. Dan Cooper of UC Irvine CTSA hub and Lisa Guay-Woodford of Children's National Medical Center/ George Washington University CTSA hub will lead this feasibility study as their optional module.

It is increasingly recognized that investigator-initiated translational research adds a unique and essential dimension to the nation's armamentarium of clinical trials. Yet the challenges facing creative and transformative early-phase concept/idea-motivated research (the hallmark of investigator-initiated clinical research) are mounting. Nowhere are these hurdles more daunting than in child-health related research.[1] CHAMP is envisioned to overcome these hurdles and enhance investigator-initiated child-health focused translational research. Following a successful feasibility project, we believe that CHAMP can be readily implemented across the CTSA. $10,000 has been committed for year one to support this important collaboration.

Figure 3. A Schematic Overview of CHAMP



The Southeast Wisconsin Alliance for Translating Research into Practice (SWATRP) is yet another model; it is a CBRN network of more than 300 family medicine, internal medicine, pediatric, nursing, and other specialties from 30 clinics. SWATRP aims to improve the health and healthcare of Wisconsin residents by encouraging the translation of scientific advances into improvements in the practices of healthcare professionals. SWATRP has successfully partnered with the primary care practices affiliated with our CTSI hub health system partner. Our hub`s CBRN (Community-Based Research Network) Database currently includes 114 medical clinics, churches, senior centers, and other community facilities, many currently involved in C/T investigation. This database provides investigators with demographic information, contact information of participating investigators, partners, or partner organizations, and investigator research interests. These two

operations provide valuable opportunities for participation in multi-site studies. The Clinical Trials Office will play a pivotal role in capitalizing on the opportunities these networks offer.

We have incorporated plans to accelerate IRB and contracting processes as described in the regulatory knowledge/support and quality and efficiency modules. We anticipate that these efforts will significantly increase efficiency and reduce the approval and processing times.

Metrics. Table 1 outlines the primary outcomes, indicators, and data sources for Multi-site Study Support. CTSI's centralized database, Waypoint©, will serve as the primary method by which process and outcome metrics will be captured and collected, along with CMS Oncore. Key performance indicators (benchmarks) for the program will be developed in year one of this proposal utilizing baseline or historical data, where available, to aid in achieving primary intended outcomes year-to-year. Quarterly dashboards will be used to summarize key performance measures and outcome data by core component (i.e. Network Resources). Dashboards and other evaluation reports will be shared with CTSI and program leadership to aid in action, decisions and discussions related to continuous quality improvement and evaluation. See Table 3 in the Recruitment section below for data on clinical trials with site activation in the first half of 2013.

Table 1: Multi-site Study Support Outcomes and Indicators

OUTCOME	INDICATORS AND MEASURES	DATA SOURCES	RESPONSIBLE PERSONS	TIME FRAME
Expand and streamline operations of existing local units (the CTO and the TRUs) to maximize efficiencies in the conduct of clinical and translational research	Number and type of services provided by CTO Number and type of investigators using CTO services (described by service) Number and type of research studies benefiting from CTO services: Time from contract received to execution Time from contract execution to date of First Accrual (FA) Study Start-up time: Time in days from date of IRB approval to first accrual Number and type of SOPs, best practices and common agreements implemented//used	Waypoint Oncore Ebridge	CTO, Regulatory, Evaluation	Annually and Quarterly
Develop new and expand existing local networks via CBRN, other CTSA hubs, etc.	Number and type of local networks Number and type of investigators partnering with the network on research projects [5 year benchmark: *increase the proportion of C/T research projects partnering with SWATRP]*	Waypoint	CBRN Director Evaluation	Annually and Quarterly
Increase the number and quality of multi-center/site research	Number and type of multi-site studies Number of investigators utilizing MARCH network	Waypoint	CTO, Evaluation	Annually and Quarterly

II. Module 6b. Recruitment of Research Participants. Lead: Jeff Whittle, MD

Delays in recruiting participants to clinical studies is a major barrier to progress in clinical research. In this section, we describe the means by which we have addressed this problem through the establishment of a recruitment unit (RU) as part of our recently established CTO, which will help support the recruitment of trial participants. We will build upon the infrastructure supporting this unit to make it operation-ready to interact with the planned CTSA Network Recruitment Centers (CT-RCs) as envisaged by NCATS. This takes a number of forms, including the creation of, participation in, and expansion of a number of hospital- and community-based consortia and databases, software optimized to aid with this goal, and our increased participation in regional groups with similar missions. The development of the CTO, described in Multisite Study Support, is key to this effort. Equally important is the development of new technological infrastructure that permits us to exploit the immense databanks available. Integrating Special Populations discusses roadblocks in our efforts to recruit from Special Populations, our prior efforts to remove these barriers, and our means to satisfy new goals to expand on these efforts. Recruitment of research study participants requires community efforts, described in Research Expertise and Methods, along with adaptations at the research sites. As described in Multisite Study Support, CTO Recruitment services will expand these CTSI efforts by supplementing and heavily marketing the availability of both ResearchMatch© (RM) and FACT. The CTO also will concentrate efforts to help promote our CTSA hub and its partners as the go-to site for the conduct of clinical trials.

Goal a. Cohort discovery using our clinical data warehouses

The i2b2 Cohort Discovery Tool provides an easy to use, self-service way for MCW researchers to query the Clinical & Translational Research Informatics Data Warehouse (CTRI-CRDW), as described in **Module 3a**. Searching such patient categories as demographics, ICD-coded diagnoses, ICD and CPT coded procedures, laboratory test results, inpatient pharmacy orders and text within clinical documents, including surgical pathology reports and radiology reports, we can identify patients who meet the inclusion/exclusion criteria of specific research studies and using HIPAA-approved means forward their unidentified information to study staff. In response to a query, i2b2 returns the approximate number of patients matching the search criteria without revealing patient identifiers or clinical data. Researchers can store their cohort searches online and later meet with staff from CTSI Bioinformatics to discuss how they might review and extract detailed clinical data on patient cohorts for research purposes. Release of data from the i2b2 CTRI-CRDW for research purposes requires MCW IRB approval, thus ensuring an additional level of security. MCW has developed web-based methods to assist honest broker in reviewing queries to manage the re-identification risk, to easily review concepts used for business sensitivity, and to confirm that the hypotheses generation for a requested study fall within the investigator's area of expertise. Through these activities, we have developed tools and secure processes for fulfilling requests for de-identified data after review and approval by the Data Request Oversight Committee (DROC) and identified data through an honest broker after approval from the IRB.

Researchers and clinicians are increasingly using EPIC collaboratively to find new and innovative ways to improve and better impact on patient care through research. The EPIC`s "Best Practice Alerts" (BPAs) function is programmable to alert clinicians of the availability of a clinical trial matching the patient's problem set and to identify potential research participants based on the pre-determined criteria. Thus, at a clinical visit, if a patient meets study criteria, the provider can facilitate further steps toward enrollment. 'Best Practice Alerts" (BPAs) use of EPIC in this manner represents a valuable EHR-based recruitment tool, particularly for those studies that require oversampling patient subgroups or stratifying randomization based upon demographic or clinical characteristics. This module is expected to enhance patient recruitment efforts and provide seamless integration of clinical and research efforts in the clinic setting.

Investigators may also use i2b2 and OnCore to search the de-identified EHR data to define an eligible cohort and once they have IRB approval they may request from the DROC a list of names and contact information on those in the EHR who meet initial study eligibility. As one decided disadvantage of RM is that it is currently unable to link with an EHR, the liaison role takes on added significance. However, in this regard we anticipate that this recruitment tool will complement our use of ResearchMatch©. OnCore software will interface with EPIC to allow the investigator to enter all study-related data. We also have obtained IRB deferral from CHW to implement an internal SHRINE instance to bridge these two health care delivery systems (see Biomedical Informatics Module). These systems also are linked to those of the 10 other academic medical institution members of the PCORnet Greater Plains Collaborative (GPC) CBRN. Collectively, these capabilities will be invaluable for cohort discovery and potential recruitment.

Goal b. Establish an effective mechanism to inform directly patients and other potential participants of available studies and clinical trials along with processes for their participation/enrollment.

i. MyChart® provides convenient and secure access to patients' health data, assuring users secure web-based access to portions of their electronic medical record via computer, smart phone, or tablet. This helpful online tool enables patients to review their current health issues and medical history, medications, immunizations and allergies, view test results, renew prescriptions, communicate with the health care team; manage appointments, and access health and appointment information for family members (with permission). Working closely with our health system partner (FH) leadership, we have established a link from MyChart that allows patients to be directed to our CTO web site and access Find a Clinical Trial (FACT) and Research Match. We are in the process of expanding this option to patients receiving clinical care at our other partner health systems. Another initiative being undertaken is to include research links and information in the monthly "Froedtert Today" magazine that is circulated to all patients and community members in southeast Wisconsin. We plan to gain access to this vast population and increase the potential to enroll community members in clinical research.

ii. The Find a Clinical Trial (FACT) database on the CTSI website was created with the research participant in mind. This site offers a simple and easy way to provide site visitors with clear and quick access to trials at our hub. Titles for each trial are presented in a non-scientific language, akin to consent form language. Additionally, a direct contact number and coordinator name are provided for ease of access. Initiated in 2014, this website will ultimately link to all our health system partners` websites to provide a comprehensive CTSI-

wide recruitment resource. Linking community-based organizations and the patient advocacy groups such as Community Health Charities (comprised of 75 organizations) with the recruitment unit is important to maximize identification and enrollment of trial participants. The CTO, RU and TRIAD navigators will collaboratively assist investigators and study staff in maximizing the use of available mechanisms for recruitment. One purpose for establishing the FACT database (and the new expanded database, below) and expanding recruitment through EPIC is to provide a source of volunteers to populate ResearchMatch© (RM). Our hub has already joined RM and will be rolling it out on its website in 2015 under the auspices of the CTO. Working through our RM Liaisons, investigators will enter studies on the ResearchMatch© website, and volunteers who meet study criteria receive an email describing studies for which they are eligible and inviting their participation. Researchers from any of our CTSI partners will be able to use RM to recruit study participants under HIPAA guidelines.

iii. Participant Recruitment from the Community: Collaborative Efforts**.** The collaborative efforts discussed in **modules 3c and 5b** will serve as a ready pool of available research participants, and our recent and planned advances in bioinformatics will provide the support to reach these individuals in transformative ways that were impossible at our institutions just a few years ago. As discussed above, the GPC will focus its research data-sharing structure on amyotrophic lateral sclerosis (ALS), breast cancer, and childhood obesity, representing one means of using these alliances to expand our pool of research participants and collaborators to perform multi-institutional research. CTSI-initiated collaborations with other CBRNs, such as PEDSnet and the CTSA at the University of Wisconsin Madison/Marshfield for the planned implementation of the i2b2 SHRINE network for the State of Wisconsin (SNOW) will represent another rich source for recruitment, as will be the CHAMP consortium to improve Child Health. MARCH will expand the diverse pools of potential research participants throughout the Midwest. Similarly, SWATRP and the CBRN provide us a firm toehold into the local Community, and MARCH permits substantial expansion of our catchment area. To expand upon the model introduced by the CE group, clinical trialists and community partners work independently. CE will broker and coordinate the efforts of those performing the clinical trials with our community partners to permit them to focus on their areas of specialization while still functioning as a collaborative team. In this "loosely coupled system" - one of the TRUs and a community partner non-profit organization will operate independently but through the mediation of the CTSI Community Engagement interface.

Metrics. Table 2 outlines the primary outcomes, indicators, and data sources for ISP. Waypoint© will serve as the primary method in which process and outcome metrics are captured and collected. Through the TRUs, data will continue to be captured via the TRU database, and integrated, through web services technology, with Waypoint©. Key performance indicators (benchmarks) for the program will be developed in year one of this proposal utilizing baseline or historical data, where available, to aid in achieving primary intended outcomes year to year. Quarterly dashboards will be used to summarize key performance measures and outcome data by core component (i.e. Research Implementation and Participation). Dashboards and other evaluation reports will be shared with CTSI and program leadership to aid in action, decisions and discussions related to continuous quality improvement and evaluation.

Table 2: Recruitment Outcomes and Indicators

OUTCOME	INDICATORS AND MEASURES	DATA SOURCES	RESPONSIBLE PERSONS	TIMEFRAME
Increase and promote strategies that minimize/decrease the delays in recruiting participants for clinical and translational research	Number and type of services offered (FACT, ResearchMatch©, etc.) and web analytics – views, etc. Number and type of investigators using recruitment services Number and type of research benefiting from recruitment services: Time from Notice of Grant Award (NOGA) to Date of First Accrual (FA) Study Start-up time: Time in days from date of IRB approval to first subject accrual Studies with adequate accrual (recruitment) Length of time spent in recruitment Number and type of BPA's #Number of data access requests and cohort searches via the CRDW and i2B2 # of investigators and studies utilizing ResearchMatch© Number patients utilizing the 'My Chart' opt-in button to participate in CT research activities Number and type of marketing tools developed	CTSI website Waypoint Ebridge Oncore EPIC	CTO, BMI, Regulatory, and Evaluation	Quarterly and Monthly

The data requested in this FOA are only available through our OnCore system which has only recently (2014) been implemented and populated with the requested data for all clinical trials that take place at our Hub. However, the system contains data for our cancer-related clinical trials for the time period inclusive of the first half of 2013. These data are presented below (Table 3). In addition, we identified 18 other phase III clinical trials for which we only have partial data (eBridge) and are, therefore, not reported here. Our Clinical Trials Office (as discussed in the multi-site section) will implement and track these data points going forward for our entire CTSA Hub which will result in higher quality and reliable data.

Table 3: Cancer Center Clinical Trials with Site Activation in the First Half of 2013 and Ancillary Data

Phase III Trials with Site Activation 1/1/13-6/30/13	Time from contract received to Execution	Time protocol rec'd by PI to IRB Appl	Time from contract executed to first patient visit	Time from IRB appl to 1st patient visit	# of planned enrollment for the LOS	Number of actually enrolled to-date	Length of study (LOS) in months
GOG-0277: A Phase III Randomized Trial of Gemcitabine plus Docetaxel followed by Doxorubicin vs Observation for Uterus-Limited, High-Grade Uterine Leiomyosarcoma	N/A	202	N/A	113	5	1	still open to accrual: 18.1
GOG-3001: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of AMG 386 With Paclitaxel and Carboplatin as First-line Treatment of Subjects With FIGO Stage III-IV Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	138	174	156	105	15	5	11.9
NSABP-B-49: A Phase III Clinical Trial Comparing the Combination of Docetaxel Plus Cyclophosphamide to Anthracycline-Based Chemotherapy Regimens for Women with Node-Positive or High-Risk Node-Negative, HER2-Negative Breast Cancer	N/A	79	196	132	40	1	6.7
CELATORCLTR0310-301: Phase III, Multicenter, Randomized, Trial Of CPX- 351(cytarabine:daunorubicin) Liposome Injection Versus Cytarabine And Daunorubicin In Patients 60-75 Years Of Age With Untreated High Risk (Secondary) AML	83	231	114	107	10	5	20.5
CELGENECC-4047-MM-007: A Phase 3, Multicenter, Randomized, Openlabel Study To Compare The Efficacy And Safety Of Pomalidomide, Bortezomib And Low-dose Dexamethasone Versus Bortezomib And Low-dose Dexamethasone In Subjects With Relapsed Or Refractory Multiple Myeloma	160	N/A	548	547	10	1	still open to accrual: 18.4
EXELIXIS-XL-184-306: A Phase 3, Randomized, Double-Blind, Controlled Trial Of Cabozantinib (XL184) Vs. Mitoxantrone Plus Prednisone In Men With Previously Treated Symptomatic Castration-Resistant Prostate Cancer	274	312	385	375	10	1	15.1
KYOWA0761-010: Open-Label, Multi-Center, Randomized Study of Anti-CCR4 Monoclonal Antibody KW-0761 (mogamulizumab) Versus Vorinostat in Subjects with Previously Treated Cutaneous T-Cell Lymphoma	269	446	26	44	25	1	still open to accrual: 19.3
MILLENNIUM-C16011: A Phase 3, Randomized, Controlled, Open-label, Multicenter, Safety and Efficacy Study of Dexamethasone Plus MLN9708 or Physicians Choice of Treatment Administered to Patients With Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis	192	253	508	480	5	1	still open to accrual: 23.8
THRESHOLD-CR-406/SARC021: A Randomized Phase 3, Multicenter, Open-Label Study Comparing TH-302 in Combination with Doxorubicin vs. Doxorubicin Alone in Subjects with Locally Advanced Unresectable or Metastatic Soft Tissue Sarcoma	161	403	77	94	10	2	11.6

III. Optional Module: Advancing Medical Product Development *through Networked Resources* (AMPD^{NR})

Lead: Daniel Sem, PhD

A. Introduction

The AMPD/NR is a southeast Wisconsin multi-institutional collaboration that will aggregate and make readily accessible essential medical product development resources within partnering institutions. The initiative is designed to overcome inefficiencies in developing innovative academic discoveries (including new drug, device, diagnostic or informatics discoveries) into health care products by more effectively linking biomedical science researchers with commercialization and development experts and potential investors. This activity aligns with the NCATS model of collaboration across and within CTSA hubs and the PCAST recommendations to develop thriving life science innovation eco-systems.

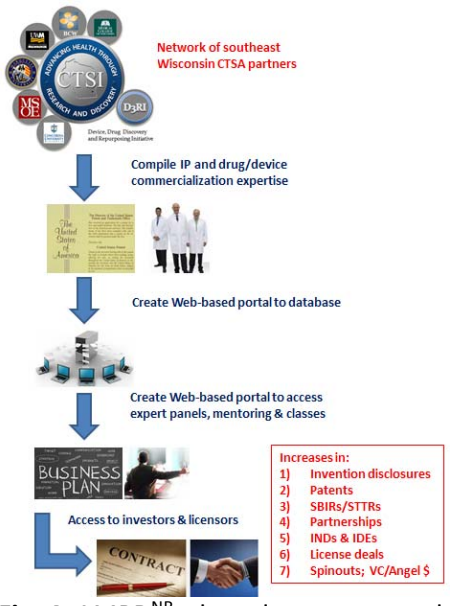


Fig. 4. AMPD^{NR}: shared resources and leverage through economies of scale to better commercialize academic discoveries.

B. Rationale

There is a pressing need for new and effective approaches that operate at the interface with industry and business development and help academic biomedical researchers transform early stage biomedical discoveries into late stage clinical development and commercial products.

Most promising discoveries in academic research centers often do not advance to products that can improve patient health. Even if discoveries are patented by an institution's technology transfer office, these assets often sit idle, unable to attract investment for proof of concept or later stage product development. Researchers may not be familiar with the development process, or have access to relevant experts who can help advise, plan and execute a developmental and commercialization path. They also lack ready access to private financing sources (esp. venture capital and angel funds), or to licensing groups in pharmaceutical companies. We will coordinate resources, expertise and business development connections across southeast Wisconsin CTSA member institutions. Coordinating these resources and making them readily accessible leverages the strengths of institutional partners and creates economies of scale, which will increase valuable product development, provide better access to strategic industry and investment partners, and therefore better translate discoveries from bench to bedside, via commercialization.

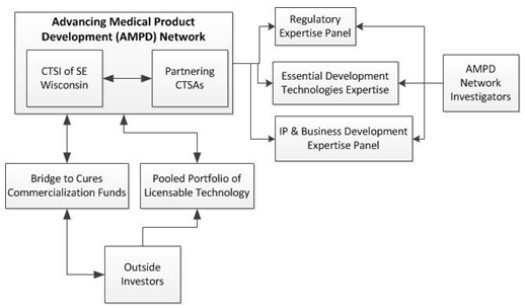


Fig. 5. Key elements of the AMPD network, which provides members with access to commercial-ization resources, and better access to investors.

C. Objective and Vision for AMPD^{NR}

To connect, coordinate and leverage the shared network of business development and commercialization expertise and connections to pharmaceutical, device and financial industries, in order to facilitate commercialization of CTSA discoveries. We aim to increase the rate of conversion of discoveries to products on the market and in the clinic – bridging the gap from patents to products.

D. Specific Aims:

1) To inventory intellectual property for commercial development at CTSA partnering institutions; to inventory commercialization and business development resources (core facilities; expertise; connections).
2) To establish a web-based interactive hub for users/clients to access networked resources from Aim B.
3) To establish a service organization to provide commercialization classes and mentoring sessions, and organize two yearly pitch and commercial partnering events targeting: (a) financing partners (venture & angel), and (b) licensing partners (e.g. pharma, device).

E. Strategy

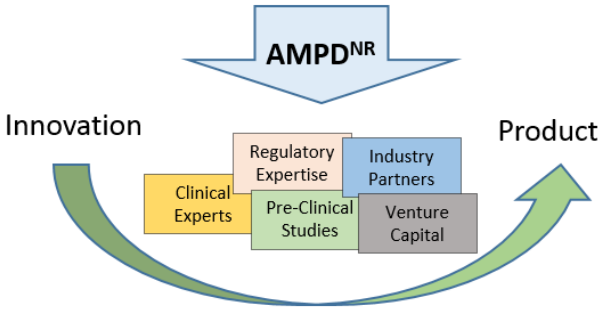
A diverse critical mass of resources, expertise and connections will be assembled and made available to investigator teams and technology transfer offices. The operating model would build upon and extend the existing regional Device, Drug Discovery and Repurposing Initiative (D3RI), which is an extension of an existing collaboration among academic institutions comprising the CTSA of SE Wisconsin. Access also will be provided to an existing national panel of health care venture capitalists associated with *Bridge to Cures, Inc.,* a SE Wisconsin CTSA inspired non-profit organization focused on early stage investments in promising healthcare discoveries.

Resources that would be connected and coordinated across the partner network include:

1) ***Translational/Clinical Expert Panels:*** Often a researcher makes a discovery that could have compelling product value. To validate such value, it is essential to test the product concept (e.g., a new drug candidate) with physician specialists in therapeutic areas to guide clinical use, competitive approaches, pricing, reimbursement, etc. Armed with this information, the researcher can engage in more productive, directed studies toward goals set by the clinical experts. Medicinal chemistry (drugs) and biomedical engineering (devices) experts also will be available. Inter-institutional panels in various therapeutic or development specialty areas will be assembled into a database, accessed by members through a shared portal.
2) ***Essential Development Technologies:*** Many scientists lack the skills and experience needed to advance their discoveries to commercial products, because the essential tools – which are common in industry – are not readily available to academics. In the drug space, technology and expertise in compound screening, medicinal chemistry (optimization for ADME-Tox, stability), formulation, process chemistry, and pre-clinical studies (acute and chronic toxicity) might not be readily available. Members will receive guidance and access to experts, cores and affiliated CROs to aid in this work.
3) ***Regulatory Expert Panels:*** The earliest possible understanding of the possible preclinical and clinical development course (and cost) of a new medical product is essential to effectively plan studies and manage resources. Clinical research and FDA regulatory experts provide this valuable information and act as a liaison to regulatory agencies, to facilitate member filings of INDs and IDEs.
4) ***Intellectual Property (IP) and Business Development Expert Panels:*** Medical products to be developed by partners must be protected by strong IP to be commercially viable. This IP must be created and marketed broadly to potential licensors in a strategic manner. Partnering institutions will share expertise and networks in these areas to build IP portfolios strategically and efficiently, which through their critical mass will more effectively attract potential partners and licensors.
5) ***Commercial Partners/Pharma Licensors:*** Many biomedical projects cannot be funded through grants and thus will require partnering with commercial entities. To facilitate this process, a database of all licensable products and technologies for CTS member institutions will be created and curated (e.g. organized by disease category), with portal access shared by all participating institutions, and made available to all corporate (e.g. pharma) partners. This large collection of licensable products creates an economy of scale that will better attract investors and licensing companies, who have specific interests.
6) ***Commercialization via University Spinout Companies:*** Funding of development projects also can occur via startup formation, funded by investment capital (venture capital, angel and state funds). To facilitate this, CTSA member institutions will have access to a shared nonprofit organization (*Bridge to Cures, Inc*.) that will provide seed funds and entrepreneurship education to researchers. *Bridge to Cures* (bridgetocures.com) operates via a unique model of matching state funds with donor or other funds; Wisconsin Economic Development Corporation (wedc.org) currently provides matching funds to donors to seed startups. This startup funding and mentoring model will be extended to the states of partnering CTSA clusters. Additional seed funds also are available through the related venture philanthropy fund, BrightStar (brightstarwi.com). In partnership with PICO (Postdoctoral industry consultants), Bridge to Cures – aided by their team of experienced life science executives and venture capitalists - will provide CEO mentoring and training for postdoctoral fellows, to lead these university spinout companies (addressing a talent gap in many CTSA cluster regions).

Several steps in the operating strategy are shown in the accompanying **AMPD/NR Operating Model.** The SE WI CTSA will serve as the administrative hub under the auspices of the executive committee of the AMPD/NR comprised of the involved institutional PIs or their designee. The AMPD/NR will work with partnering institutions to inventory their relevant resources and make them available to the consortium, to create the *resource portfolio*. Users/clients will engage the AMPD/NR to access resources.

Figure 6.



F. Business Model - is based on collaboration and complementation to maximize capabilities

Each partnering institution will contribute both in-kind and cash to the consortium as follows.
Cash contribution: minimal (to be decided) to support essential expenses.
In-kind contributions: substantive, and include participation in expert panels.

G. Metrics of Success

1) Increased numbers of invention disclosures, patents and product development successes (IND and IDE filings) are expected from each member institution, due to resources provided by **AMPD/NR.**
2) Increased numbers of licensing agreements and commercial partnerships also are expected.
3) Increased numbers of new ventures (spinout companies) levels angel/venture/state financing dollars. Due to increased startups formed, increased SBIR/STTR grants will be secured from each institution.

H. Initial Projects

1) Portal of experts - for panels (regulatory; development; IP; business development)
2) Portal of CTSA development resources (cGMP manufacturing; CMC; formulation; PK-ADEM-Tox)
3) Portal of CTSA member institution intellectual property (licensable assets)
4) Courses/seminars; entrepreneurship education; CEO training for postdoctoral fellows (PICO)
5) Corporate (and pharma) Partnering Fair

Venture fair; pitch to *Bridge to Cures* venture capitalist panel (OrbiMed, Technomark, Mercury, etc.)

NRSA TRAINING CORE. **LEAD: PD/PI David Brousseau, MD, MS**

The START Program has three program components:

1. **Leverage existing MCW Pipeline Programs to mentor highly qualified high school and undergraduates of diverse backgrounds towards career destinations in clinical and translation research as MDs, PhDs, and MD-PhDs.**
2. **Support one year of research training for medical, graduate, and MD-PhD students and MD-fellows in clinical and translational research towards MS or PhD degrees.**
3. **Mentor START Program graduates throughout their research careers at MCW.**

The Objectives of the START Program are to:

- Coordinate with the current pipeline of established high school and undergraduate programs at MCW to mentor highly qualified young students of diversity for careers as clinical and translational scientists.
- Leverage the **Physical Scientist Pathway (PSP), a flagship professional development program at MCW** that allows medical students protected curriculum time to individualize their medical training, by exploring a research career path. PSP trainees work with peers and faculty, building on the foundation of medical school experiences, to pursue an area of common interest in greater depth. The PSP provides the foundation for the MD-MS degree where medical student take a year of research between the M2-M3 years of medical school to complete a thesis research project, leading to the MS degree.
- Provide one year of stipend for medical students, graduate students and MD-fellows to conduct research and develop fundamental, quantitative skills involved in clinical and translational research as components of a PhD and MS degree.
- During the year of research, students participate in workshops that teach grant writing, manuscript writing, and other professional development skills, including best practice strategies to optimize communication skills.
- Provide Team Science experiences for students in the program as a vertically integrated training experience. Medical and graduate students conducting clinical and translational research will matched with an MD-fellow to experience T3-T5 types of research projects directed to improve the health of human populations. This will include activities with high school and undergraduates from our pipeline programs, to reinforce the impact that clinical and translational research has on human populations within our community.
- Trainees participate in bi-annual conferences to present their current studies in a team-based environment.
- Use the Individual Development Plan (IDP) to optimize the training experiences of our trainees.
- Organize a workshop with the trainee's mentors to establish best practice mentoring for the trainees.
- Mentor graduates of START Program for successful careers as scientists and physician-scientists at MCW.
- Sensitize the research community at MCW to promote an environment that fosters an "all inclusive" atmosphere for scientific discovery.

The START Program will support one year of training in clinical-translational research towards the MS or PhD degree. Trainees will commit at least 80% research effort for one year with the possibility of extending their research experience for a second year. Within our CTSI, trainees have numerous opportunities to study in research programs that integrate basic scientists and clinicians who address important questions in medicine. We will leverage existing research programs, such as the "Clinical Genome Wide Sequencing Core for the Undiagnosed Disease Network: PIs, Howard Jacob PhD and David Bick, MD" who use "whole genome sequencing" and "wet lab assessment" to define the genetic bases for unknown childhood diseases as sited for research projects that provide a translational environment for research training.

I-B How training core will relate to current training activities at the CTSI participating institutions The START Program is unique within the institutions of the CTSI, being the only training program that provides stipends to support trainees to complete their clinical and translational research studies towards the completion of MS or PhD degrees. Working with the Graduate Schools within the institutions of the CTSI, the START Program will provide an integrated research experience that emphasizes Team Science experiences, which are often difficult to achieve within the curricula of traditional biomedical research programs. The Medical School at MCW provides a subset of medical students an opportunity to pursue an "Honor's in Research," based on extended research participation. However, the accumulated research training experience is limited to 16 weeks, divided between two years, and does not provide sufficient time to develop independent investigator skills.

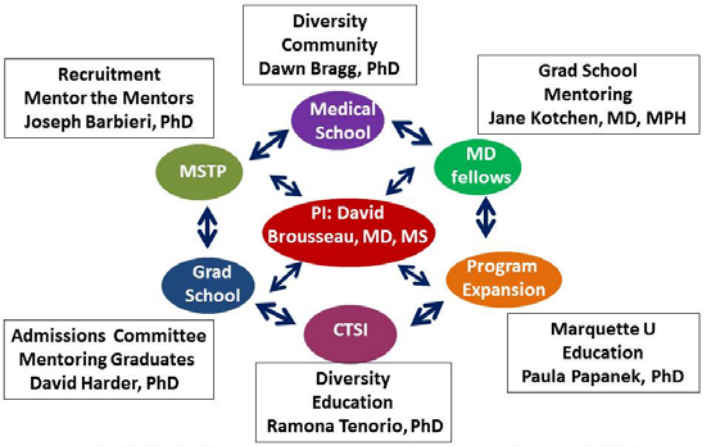


Figure 2. START Program Leadership Committee. START Program leadership meets monthly to coordinate programmatic and academic activities.

II. Program Plan

II-A Program Administration. The administrators of the START Program include established leaders of the research and training programs at MCW and Marquette University, as well as junior investigators who provide academic expertise to optimize our students training experiences. Dr. Brousseau will Chair the Leadership Committee, which comprises the academic directors of the program that will participate in START and CTSI leadership who are involved in education and MCW pipeline diversity programs (**Figure 2**).

II-A-1 Project Leadership:

David Brousseau, MD, MS; PI and Director of the CTSI START Program Dr. Brousseau is Professor of Pediatrics at MCW and Director of both the Physician Scientist Pathway and the MD-MS Clinical and Translational Science 4-year dual degree program at the medical school. Dr. Brousseau will oversee the academic and administrative efforts of the START Program and be the administrative mentor for trainees in the research component of the Program. He also is an active mentor in the MS program for subspecialty Fellows. Dr. Brousseau has mentored **six** Pediatric Emergency Medicine fellows to the MS degree. As described above, medical students and subspecialty Fellows are two of the four portals of entry into this START program, and Dr. Bousseau's experience in these areas will be vitally important to the success of the program. Dr. Brousseau is also the founding Director of the Physician-Scientist Pathway, a professional pathway for ~ 80 (annual) MCW medical students who conduct T1-T4 research during their M1-M3 years. We anticipate that a subset of these students will continue these research experiences and conduct a year of clinical translational research to complete an MD-MS in five years. Dr. Brousseau has 56 peer-reviewed publications, been federally funded for research (with both R and U grants) and serves as the site PI in a multi-center research network. His research emphasis includes studies on "Hospital care for acute sickle cell disease-related visits" and "Medications that affect pediatric sickle cell pain crisis" linked to the stated outcomes of our START Program. These studies provide advanced training that aligns with CTSI goals of advancing therapeutics, clinical interventions and behavioral modifications to improve health. Dr. Brousseau will lead the recruitment of MD-fellows into START Program.

David Harder, PhD, Associate Director of the START Program. Dr. Harder is Professor of Physiology. Dr. Harder also is Associate Dean for Research Mentoring for clinical and basic scientists and Director of the Medical Student Summer Research Program. Dr. Harder will lead the Trainee-Mentor Evaluation Committee and the Graduate Mentoring efforts. Dr. Harder is the PI on a T32 training grant for post-doctoral fellows that is in year 21 and PI for a T35 training grant (in year 32) supporting 24 of the medical students participating in the Summer Research Program noted above. As the Director or Mentoring for our CTSI, Dr. Harder is developing research and educational Programs between MCW and our partnering institutions, Marquette University, University of Wisconsin at Milwaukee, the Milwaukee VA Medical Center, and the Blood Research Center of Southeast Wisconsin. Dr. Harder has published 260 peer-reviewed publications that include studies on "the protective effect of astrocyte-derived arachidonic acid metabolites on cell injury in cell culture" and how

phosphatases modulate myogenic responses in rat cerebral arteries. Dr. Harder is the recipient of the Carl J, Wiggers Award Cardiovascular Section from The American Physiological Society.

Joseph T. Barbieri, PhD, Associate Director of the START Program, Dr. Barbieri is Professor of Microbiology and Molecular Genetics and the Director of the Medical Scientist Training Program (T32-MSTP, MD-PhD Program). Dr. Barbieri will lead the Mentor the Mentors Meetings and direct recruitment efforts. Dr. Barbieri has been Director of the MSTP since 2005; there are currently 44 students in training. He has mentored 21 students to the PhD and 4 students to the MD-PhD. Dr. Barbieri has published 144-peer reviewed publications. He studied Mechanisms of Bacterial Toxin Action, which has been funded by the NIH since 1987. He has 3-US Patents and one licensed product. Dr. Barbieri will lead the recruitment efforts for the START Program, at both local (high school and undergraduate institutions) and national recruitment venues. Dr. Barbieri is active in both local and national recruitment efforts for the MSTP. This is a natural link, since both training programs target highly qualified students of diverse backgrounds who have a passion for science and service to the community.

Dawn Bragg, PhD Associate Director of the START Program holds three appointments at the Medical College of Wisconsin. Dr. Bragg will lead diversity recruitment efforts within the pipeline programs. As Associate Dean for Student Affairs-Diversity, Dr. Bragg has spearheaded increasingly successful efforts to identify and recruit potential participants from diverse ethnic and racial populations as well as students from economically, culturally or socially disadvantaged backgrounds. Her exceptional interpersonal skills and sensitivity are instrumental in establishing a special rapport and trust with these potential candidates. Dr. Bragg directs the privately funded *Apprenticeship in Medicine (AIM)* and the *Research Opportunities for Academic Development in Science (ROADS)* programs targeting minority high school students. Dr. Bragg also is Director of Educational Services in the Office of Academic Affairs and Associate Professor of Pediatrics (Medical Education). In this capacity, she contributes educational statistics and outcomes evaluation expertise to the medical education program and residency programs through the Office of Academic Affairs, the Office of Graduate Medical Education and the Departments of Pediatrics and Family Medicine. She has authored or co-authored 116 publications. Dr. Bragg additionally serves as an administrative member of MCW's Diversity Committee, which oversees the development and implementation of institutional diversity initiatives across the campus and within the community.

Jane Morley Kotchen, MD, MPH, Professor of Medicine and the PhD Program in Public & Community Health at MCW. Her research focus is in epidemiology. She has a long history of NIH-funded research, including a community-based project of High Blood Pressure in the Young, and community-based hypertension control projects in rural Kentucky and in Chicago/Milwaukee. She is the site Principal Investigator for the long standing NIH Women's Health Initiative. She also serves as the Principal Investigator for a 5-year community-based research project focused on cardiovascular risk reduction in a rural Wisconsin county. She serves as Director of the CTSI Master of Science in Clinical and Translational Science Program, which provides clinical research training for both pre-doctoral and post-doctoral students. In addition, since its inception in 1999, she has served as the Director of the CTSI Clinical Research Scholars Program (formerly K30), a two-year research career development program for junior faculty, which also provides research training for the CTSI KL2 Scholars. Dr. Kotchen has been a reviewer for both the NHLBI K23 and K08 clinical research career development grant applications.

Paula E. Papanek, PhD, MPT, ATC/L Associate Director of the START Program. Dr. Papanek is Associate Professor of Exercise Science in the Department of Physical Therapy, Director of Exercise Science, Dr. Papanek will lead activities to expand the scope of the research opportunities within the START Program. Dr. Pananek is the Director of Graduate Studies in Clinical and Translational Rehabilitation Science at Marquette University, and Coordinator of the Physical Therapy PhD Program. Dr. Papanek's graduate work and post-doctoral studies animal models of hypertension and maintains active collaborations with the Cardiovascular Center and the Department of Physiology at MCW. Dr. Papanek has published 27 peer-reviewed publications. These studies address disease prevention and wellness in human populations. Over the last 5 years, Dr. Papanek has been involved in community initiatives directed at exercise and wellness in both obese geriatric and youth populations. These studies align with the START Program, providing clinical interventions and behavioral modifications to improve health.

Ramona Tenorio, PhD Associate Director of the START Program, Dr. Tenorio is the clinical coordinator in our CTSI and has formal experiences coordinating activities in responsible conduct of research at MCW. Dr. Tenorio will lead the education of trainees in issues of diversity as members of our health care profession. Dr. Tenorio is an applied medical anthropologist with over 9 years of experience in applied health research. As the Program Manager of the CTSI Pilot and Collaborative Clinical and Translational Research Grants Program at MCW, Dr. Tenorio has increased funding across the translational continuum (T1-T5), and increased the depth of interdisciplinary and inter-institutional collaborations in team science. Dr. Tenorio is a recent PhD graduate of the University of Wisconsin-Milwaukee in Anthropology "*Dissertation:* Medicina Del Barrio: Shadow Medicine among Milwaukee's Latino Community'. Dr. Tenorio's research focuses on Applied Medical Anthropology, Immigration and Health, Latino lay healing practices in the United States and Mexico, and Gender Issues.

COMMITTEES

Admissions Committee is composed of the participating leadership of the START and several members of the CTSI faculty. Dr. Brousseau will be the leader of the admissions committee. The committee will meet monthly to review applicants. Applicants will be ranked based upon their didactic scores and research proposals. Medical student applicant review also will consider progress during their summer research between the M1-M2 years. Applications will be accepted between August 1st and December 1st. At the December leadership meeting, applications will be reviewed and ranked. Applicants will matriculate into the START Program in January to begin 1 year sponsored research projects (July 1 - June 30) in next academic year.

Trainee-Mentor Evaluation Committee composed of directors from the medical and graduate schools, and residency program directors from participating CTSI institutions that will evaluate the research and professional development of the trainees in the START Program and evaluate the trainee mentors to determine how effectively the mentor is contributing to the trainee's research and professional development.

II-A-2 Relate strengths to proposed management of the START training core

The strengths of the proposed management of the training core lie in the participating leadership of the START. The leadership of the START Program is comprised of the directors of the training programs from which potential trainees will enter the Program. This relationship provides the greatest likelihood of success, as these directors currently mentor trainees towards MS or PhD degrees and mentor young students and faculty towards successful careers in clinical and translational research at MCW.

II-A-3 Strategy and administrative structure to oversee and monitor the START core The START Leadership (the Director and Associate Directors) will meet monthly to discuss programmatic issues and opportunities to enhance the students training experiences. More frequent meetings will be held when needed to address specific issues. The Admissions Committee and the Trainee-Mentor Evaluation Committee will meet monthly throughout the year. The CTSI will provide administrative support for the recruitment and matriculation of trainees into the program and for acquiring outcomes data on the graduates of the START Program.

II-B Program Faculty

II-B-1 Core Faculty/ Mentors

a) Clinical and Translational Research Investigators The core faculty and mentors for the START Program are members of the Medical College of Wisconsin (MCW) faculty or affiliates from CTSI participating institutions. MCW is the largest private academic medical center in Wisconsin and is located in the Milwaukee Regional Medical Center along with our hospital affiliates. MCW has ~1,600 full time faculty and ~ 3,450 full time staff. 2013 marked the 120th anniversary of the institution's founding. In 1967, Marquette University terminated sponsorship of the medical school, which continued as a private, freestanding institution named the Medical College of Wisconsin (MCW). MCW has ~15,000 alumni. The Mission of MCW is to: discover and translate new knowledge in the biomedical sciences, provide cutting-edge, interdisciplinary and compassionate clinical care of the highest quality, and improve the health of the communities we serve. This mission fits well within the charge of the START programs. MCW is one of the fastest growing academic research medical centers in the US.

Table 1 Shows the Membership of Participating Departments/Programs at MCW. A PhD degree in clinical and translational research is awarded for scholarship with a focus in biochemistry, biophysics,

biostatistics, cell and developmental biology, microbiology and molecular genetics, pharmacology and toxicology, physiology, and functional imaging, a joint PhD program with Marquette University. MCW is one of a few institutions which offer a PhD in Public and Community Health. MCW's research enterprise is focused on strategic, prioritized areas of research involving interdisciplinary collaboration among scientists and physicians with the goal of rapidly translating discoveries to advance patient care. Graduate students obtain their PhD studying within one of six basic science departments: Biochemistry, Biophysics, Cell Biology & Neuroscience, Microbiology & Molecular Genetics, Pharmacology & Toxicology, and Physiology. The MS in Clinical and Translational Science is awarded through the Graduate School of Biological Science at MCW. In 2013, twelve MS awards were given in Clinical and Translational Science were awarded. One awardee, Andrea K. Morrison, MD trained with Dr. Brousseau in Pediatric Emergency Medicine. Dr. Brousseau is the PI of this START TL1 application. Dr. Morrison's thesis was titled; "Caregiver Low Health Literacy is Associated with Non-Urgent Emergency Department for Fever". The focus of the scholarship in the MS in Clinical and Translational Science that were awarded in 2013 included studies in Pediatrics, Hematology/Oncology, Gastroenterology, Emergency Medicine, and Medicine.

b) **Table 2** shows the Faculty Track Record for faculty who will participate in the START Program. Of the 106 faculty, 29 are faculty administrators (committee members) and/or professional mentors and 89 are research faculty, potential mentors of trainee's research projects. Thirteen faculty have both administrative and research mentoring positions. Among these 89 research mentors; 50 are Professors, 23 are Associate Professors, and 11 are Assistant Professors. Forty-six faculty have primary appointments in Research Centers or Affiliated Research Institutes, which extends clinical and translational research topics for our trainees to study beyond those topics studied by faculty in the basic science departments. Within the MCW academic campus, ~160 faculty in the Graduate School of Biological Sciences may serve as MS or PhD mentors.

c) **Table 3** shows Faculty research supported by **11** training grants at MCW that span the research interests of our faculty including: Vision Science, Physiology, Acquired and Congenital Cardiovascular Disease, Hypertension and Vascular Biology, Anesthesiology, Aging and Injury Research, HIV Prevention, and Gastroenterology Research. There are 34 faculty who are listed on multiple pre-doctoral or post-doctoral T32 training grants who are also participants in the START Program. This is evidence for the collaborative nature of the research of our faculty. Expanding collaborative research efforts and expertise within the research centers and basic science departments is a top MCW priority. In FY **2012-13** faculty received more than $140 million in external support for research, of which ~ $90 million was in NIH funding. MCW ranks in the top third of medical schools receiving NIH funding. MCW is one of the highest-ranking medical school for NIH funding per number of faculty (ranking 3rd in 2013), attesting to the productivity and research quality of our faculty.

Table 4 shows Faculty research support. Thirty-six of the potential research faculty mentors currently have multiple active NIH grants with the remaining potential faculty mentors at the rank of Professor or Associate Professor having one active NIH grant.

Table 5 shows the faculty experience in training students. Of the 89 potential faculty mentors, 72 have graduated multiple students, 9 have graduated one student, while 8 faulty have not graduated a student, but currently have a student in training.

d) Diversity of the faculty/mentor pool The developmental history of MCW as first part of a private Jesuit University and then as a free standing private Medical School is one of great sensitivity to the peoples it serves, many of whom are in poor urban areas. MCW is the largest provider of Milwaukee's underserved communities, and carries a heavy charitable load. As such, our faculty has a unique and realistic philosophy with respect to the need to bring state of the art medical care to its providers and patients. While we have relatively few minority faculty, our sensitivity to the unique ethnic makeup of our patients and their needs cannot be overstated. We view a successful START Program as contributing to an increase in the diversity of the scientific and physician scientist make-up of the next generation of MCW faulty.

e) Complementary expertise and experiences of the faculty Many of the faculty mentors are collaborators on NIH funded grants and co-authored PubMed cited publications. A document in the appendix is a non-inclusive listing of publications co-authored by the mentors listed in **Table 2 (Appendix #2 Co-authorship among START mentors, 89 publications)**. MCW also maintains a Faculty Collaboration

Database (FCD) (http://fcd.mcw.edu/) to foster collaborations between faculty members MCW and other CTSI participating Institutions, including UW-Milwaukee and Marquette University. The FCD supports research advances, patient care needs, and educational excellence. Basic demographic information as well as faculty grants are included in the faculty profiles. Other information such as published articles, leadership positions, mentoring availability, educational expertise, clinical expertise, community partnerships are parts of the profile that faculty can add to the FCD.

A brief description of the Basic Science Departments, Research Centers, and Affiliated Medical Sites where our trainees will conduct a year of clinical and translational research follow:

MCW Basic Science Departments The basic science departments are the academic foundation of the research community of the Graduate School of Biomedical Sciences at MCW. Each department possesses academic specialties, which provide unique graduate training opportunities for MS. MD, MD-PhD trainees that lead to an MS or PhD, with an emphasis in biochemistry, biophysics, cell biology and neuroscience, microbiology, pharmacology, or physiology. Each trainee follows the guidelines of their specific basic science department and the Graduate School of Biomedical Sciences to complete the degree requirement for the MS and PhD, while continuing clinical exposure and professional development through programmatic facilitated activities. The following sections provide an overview of several of the Integrated Research Centers and select faculty who are active in our MS, PhD, and MD-PhD as mentors, potential mentors, or who have recently joined our faculty. There are six basic science departments at MCW. **BIOCHEMISTRY** Clinical, translational and basic research interests in the Department of Biochemistry span the spectrum of modern biochemistry from the study of stem cell development to the analysis of protein structure. The unifying theme of the Biochemistry Department is an interest in the molecular aspects of biological processes, utilizing X-ray crystallography, NMR spectroscopy, mass spectrometry, and cell biological approaches. **John Corbett**, PhD, recently joined the department as Professor and Chair. Dr. Corbett's research addresses the factors that influence the function and survival of pancreatic beta cells in the context of type 1 and type 2 diabetes mellitus [1]. **BIOPHYSICS** The Biophysics doctoral program provides two main tracks of study: the Magnetic Resonance Imaging track and the Molecular track. The Electron Paramagnetic Resonance (EPR) Center, located within the Biophysics program, is one of the largest EPR facilities in the US. Faculty research interests include studies in free radicals and nitric oxide, spin labeling to study protein structure, paramagnetic metal ions as a structural determination of active sites, and instrumentation, including EPR, ESR, functional MRI, and molecular imaging. **Balaraman Kalyanaraman,** PhD (Professor and Chair) applies EPR to define the role of free radicals in signal transduction and apoptosis [2]. **CELL BIOLOGY, NEUROBIOLOGY, AND ANATOMY** Faculty research emphasizes developmental biology, neurobiology, and stem cell research. Developmental studies focus on stem cell biology to address growth, regeneration and transcription mediated pathways in heart and liver development, and muscle atrophy and plasticity. Neurobiology spans the major issues related to vision, including plasticity in the visual cortex and fMRI of the visual system. **Joseph C. Besharse,** PhD (Professor and Chair) studies the cellular and molecular basis of circadian rhythm in peripheral oscillators and transduction machinery in retinal photoreceptors [3]. **MICROBIOLOGY AND MOLECULAR GENETICS** Faculty utilize virology and bacteriology systems to define molecular mechanisms of pathogenesis and cellular processes of microorganisms and the host during infection. **Paula Traktman**, PhD (Professor and Chair) studies the molecular biology of the Vaccinia (Pox) virus replication and the role of virally encoded kinases and phosphatases within the infectious cycle and virion morphogenesis [4]. **The Committee on Immunology** is an open community of faculty dedicated to research in immunology with research interests that range from studies on the modulation of the immune response that prevent autoimmune diseases, to studies on immune response activation to recognize infectious disease agents and cancer. Members include researchers at MCW, the Blood Research Institute, and Children's Hospital of Wisconsin. The Committee coordinates seminars by visiting scholars, participates in graduate and medical education, and sponsors research meetings. The Committee sponsors a monthly seminar series, a weekly journal club, and research-in-progress. **Calvin B. Williams,** MD PhD (Associate Professor of Rheumatology and Associate Program Director of the MSTP and Research Director of the Children's Research Institute) studies immune modulation by Foxp3 T cells [5]. **PHARMACOLOGY AND TOXICOLOGY** Faculty conduct research in cardiovascular- and neuron- pharmacology, neurotoxicology, and molecular pharmacology that involves cellular and molecular pharmacology and signal transduction. Several of the faculty utilize mass spectrometry to identify small molecules and posttranslational modifications. **William B. Campbell**, PhD (Professor and Chair) studies endothelial cells as components of the lumen of blood vessels, contact smooth muscle cells, and circulating

blood cells, to determine how these cells release soluble mediators of cell physiology, including metabolites of arachidonic acid [6]. **PHYSIOLOGY** is one of the premier comprehensive physiology departments in the US, ranking 3rd in NIH funding (2013), with programs in cardiovascular, renal and respiratory physiology, physiological genomics, proteomics and computational biology. Program growth is based on the close interaction of the Physiology Department with four major MCW Research centers: Cardiovascular Center, Biotechnology and Bioengineering Center, Human and Molecular Genetics Center, and Kidney Research Center. **Allen W. Cowley, Jr.**, PhD (Professor and Chair) studies the impact of arterial pressure on the production of oxidative stress and renal injury in the renal medulla of hypertensive rats. Other collaborative studies include the determination of the genetic and physiological basis of protection from salt-induced hypertension [7].

RESEARCH CENTERS AT MCW Growth of collaborative basic science and clinical and translational research at MCW has developed around our centers-based research themes. These Centers encourage multidisciplinary research across departmental boundaries, providing training experiences for our MS, PhD, and MD-PhD students where they conduct mechanistic research with center faculty holding primary or secondary appointments in the basic science departments. The **Research Centers** comprise faculty with many areas of expertise, including:

Federally Designated Centers

- National Biomedical Electron Paramagnetic Resonance
- National Center for AIDS Intervention Research
- National Center for Systems Biology
- National Clinical and Translational Science Institute
- National Injury Research Center
- National Research Center of Excellence in Pediatric Nephrology
- Wisconsin Center of Excellence in Genomics Science
- Wisconsin CIREN (Crash Injury Research and Engineering Network) Center

International Center, Centers and Institutes

- Cancer Center
- Cardiovascular Center
- Center for Bioethics and Medical Humanities
- Center for Imaging Research
- Center for Infectious Disease Research
- Center for Patient Care & Outcomes Research
- Digestive Disease Center
- Human and Molecular Genetics Center
- Center for International Blood and Marrow Transplant Research
- Institute for Health and Society
- Neuroscience Research Center

CARDIOVASCULAR CENTER The Cardiovascular Center (CVC) brings together more than 20 investigators within the CVC, and more than 100 clinicians and 50 basic scientists from various MCW departments, who are studying the prevention, detection, treatment and cure of cardiovascular disease as a "Specialized Center for Research on Hypertension". **Ivor Benjamin** MD, Chief of Cardiovascular Medicine and Director of the Cardiovascular Center, joined the MCW faculty from the University of Utah where he served as professor of Cardiology and Biochemistry and director of the Laboratory of Cardiac Disease, Redox Signaling and Cell Regeneration. Dr. Benjamin studies inheritable cardiac failure and myocardial infarction [8]. He serves on the National Advisory Board of the NHLBI. **David L. Mattson**, PhD (Professor) studies the role of immune cells in the development of hypertension and kidney disease [9]. **HUMAN AND MOLECULAR GENETICS CENTER** The Human and Molecular Genetics Center (HMGC), established in 1999, has created a new Individualized Medicine Institute (IMI) in conjunction with the Department of Pediatrics at the Children's Hospital of Wisconsin to develop future individualized medicine and genetic research that will translate basic research to clinical medicine. The HMGC was the first center to offer complete whole genome sequencing (WGS), from patient consent through the return of clinical results. These studies are a collaborative effort between clinical investigators led by **David Bick**, MD (Professor of Pediatrics) and basic scientists led by **Howard Jacob**, PhD (Professor of Physiology) [10]. **FUNCTIONAL IMAGING RESEARCH CENTER** The Functional Imaging Research Center investigators at MCW demonstrated that magnetic resonance imaging could be used to measure brain function by functional MRI (fMRI). MCW fMRI faculty continue technological advances of fMRI and use this technology to understand brain systems activated when healthy individuals perform sensory, motor and cognitive tasks. The Center oversees the operations of two dedicated MRI research scanners on campus. **Jeffery Binder,** MD (Professor of Biophysics) studies Functional Magnetic Resonance Imaging during auditory language processing [11]. **CANCER CENTER** The Cancer Pavilion integrates MCW cancer services through partnerships with researchers and physicians at MCW, Froedtert Hospital, Children's Hospital of Wisconsin, Clement Zablocki VA Medical Center, and the Blood Research Institute. **Ming You**, MD, PhD (Director) studies cell-surface protein expression in endothelial cells and their

contribution to migration, apoptosis and proliferation [12]. **MAX MCGEE NATIONAL RESEARCH CENTER FOR JUVENILE DIABETES** The Max McGee Research Center addresses the molecular basis for type 1 diabetes using functional genetics, combined with genetic mapping to identify potential molecular pathways for therapeutic intervention. Children's Hospital of Wisconsin is home to one of the largest diabetes treatment programs in the nation, currently following > 1,200 children with diabetes. The Center is involved in projects to map the genetic basis of adult-onset type 1 diabetes and on gene expression in T cells and dendritic cells [13]. **Martin Hessner**, PhD, is the Director of the Max McGee Research Center **NEUROSCIENCE RESEARCH CENTER** The Neuroscience Research Center was founded in 2010 with the goal of enhancing neuroscience research at MCW. The overarching goal is to use a team approach to tackle neurological and psychiatric disorders. **Cecilia Hillard**, PhD (Professor and Director) utilizes molecular approaches to dissect the basis for drug addiction to understand how steroids influence endocannabinoid content and cannabinoid receptor binding [14].

AFFILIATED MEDICAL SITES. MCW physician practices essentially span every specialty and subspecialty of medicine. Each year, MCW providers, physician assistants, nurse practitioners and psychologists care for more than 425,000 patients, representing more than 1.6 million patient visits in 2012-2013. MCW providers practice at three major affiliates - Froedtert Hospital, Children's Hospital of Wisconsin, and the Zablocki VA Medical Center, as well as at other collaborative hospitals and clinics in the Milwaukee area. Together, this research and clinical environment provides our MS, MD, and MD, PhD trainees a greater breadth of collaborative and interdisciplinary research opportunities than are available in the typical basic science department. **Children's Research Institute (CRI)** Investigators at the CRI advance state-of-the-art pediatric health care through basic and translational research programs. The focus is to find life-saving discoveries and cures in the diseases that affect children as well as interventions that enhance quality of life for children and families living with chronic health conditions. The CRI is part of the Children's Hospital of Wisconsin and is affiliated with the MCW. Over the past 8 years, the Department of Pediatrics, a partner with the CRI, has risen from 37 to 21 in NIH funding. **Blood Research Institute (BRI)** Basic and clinical scientists at BRI have made significant discoveries leading to improvement of diagnosis and care of patients. The BRI's Diagnostic Laboratories and Blood Services provide further opportunities for collaboration in development and use of diagnostic tests and access to blood samples and related databases. Research programs at the BRI include; Transfusion Medicine Stem Cell Biology and Hematopoiesis, Immunobiology, and Thrombosis and Vascular Biology. The BRI houses a state-of-the-art facility that gives investigators access to cutting-edge research equipment and related specialized services. The faculty at the BRI include: 16 PhDs, 11 MDs, and 4 MD-PhDs who have mentored and continue to mentor our MS, MD, MD-PhD trainees to solve mechanistic research in vascular biology in a translation environment.

II-B2 Provide a plan to ensure faculty provides successful guidance to trainees. One goal of the START is to establish a "Mentor the Mentor" program to facilitate the exchange of best practices for the optimal training of our students throughout the START pipeline. Mentors of our trainees will participate in a monthly workshop/forum lead by Dr. Barbieri, based upon his experience in matching mentors with MSTP trainees and facilitating student-training plans written by specific mentors. Each forum will focus on the mentoring plan of an individual trainee written by an attending mentor. Mentors will present the training plan and the rationale for specific activities pursued during the research year. The open forum should facilitate exchange of best practice based on feed back by other preceptors and will be incorporated into a document to each mentor and supplied to future mentors in our program for reference on best mentoring practices.

II-B3 Describe mentor appointment, removal, evaluation plan. Mentors are appointed to START program based upon a track record of training experience and external funding. Professors and Associate Professors will possess current external funding to support the studies of the trainees in their programs and will have mentored trainees to the MS or PhD degree. Assistant Professor are encouraged to participate as mentors based upon approval by the Chairperson of their academic appointment. Should an Assistant Professor be chosen as a mentor, a senior faculty will be appointed by the START Program leadership as a co-mentor. Faculty who do not maintain external funding will be removed from the mentoring pool.

The **Trainee-Mentor Evaluation Committee** (TMEC) will also provide an independent evaluation of the mentor and trainee**.** The TMEC will be composed of leaders of the START, program directors from the medical and graduate schools, and residency program directors from participating CTSI institutions. The TMEC will evaluate the progress of trainees and determine the contributions made by mentors in directing students to complete their research projects and to assure that students have acquired professional skills commensurate with the academic rank (MS or PhD degree). The evaluations will assess the mentor's training plan for their student. The goal of this evaluation is identify potential conflicts between the trainee and mentor, evaluate student's progress, and determine the mentor's ability to direct the student to overcome potential barriers. The TMEC will comprise three faculty who will be identified uniquely for each Trainee-Mentor pair.

C Proposed Training

C-1 Program overview The START has three components for proposed training that will capitalize on established programs within the CTSI institutions to:

1. **Leverage existing MCW Pipeline Programs to mentor highly qualified high school and undergraduates of diverse backgrounds towards career destinations in clinical translation research as MDs, PhDs, and MD-PhDs.**
2. **Support one year of research training for medical, graduate, and MD-PhD students and MD-fellows in clinical and translational research towards MS or PhD degrees.**
3. **Mentor START Program graduates towards successful research careers at MCW.**

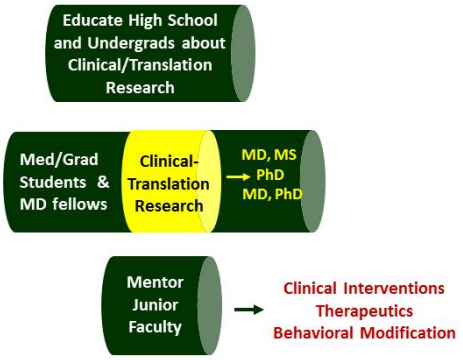


Figure 3. The START TL1 Program. There are three components of the TL1 START Program, Education, Training, and Mentoring Graduates: 1) **Education**, utilizing existing MCW pipeline programs, highly qualified students from diverse backgrounds will be exposed to careers in clinical and translational science. 2) **Training**, START will support one year of research for trainees to complete MS and PhD degrees in clinical and translational research, and 3) **Mentoring Graduates**, junior faculty will be mentored throughout their careers at MCW.

1) Leverage existing MCW Pipeline Programs to mentor highly qualified high school and undergraduates of diverse backgrounds towards career destinations in clinical translation research as MDs, PhDs, and MD-PhDs. The START Program will mentor students within established pipelines at MCW for high school and undergraduates programs. Pipeline Programs are briefly described below:

High School Students and Community: High school students participate in a variety of privately funded research oriented programs at Institutes within our CTSI.

- **Research Opportunity for Academic Development in Science (ROADS) program** (initiated in 1990) enables a selected group of 7-10 highly qualified, science-minded Milwaukee high school students from diverse backgrounds to participate as research fellows for seven weeks in the laboratories of Medical College investigators. This program is designed to provide participants with a meaningful experience in a health-related field and to stimulate their interest in careers in science, medicine and biomedical research.
- **Apprenticeship in Medicine, (AIM) program** (initiated in 1989), similarly targets 12 multicultural/disadvantaged high school students yearly to participate in an intensive six-week program of clinical hands-on experiences that promote greater understanding and appreciation of common, important medical problems that impact their community. AIM encourages students to continue their education beyond high school and college and introduces students to components of medical care in our community.
- **American Chemical Society (ACS) Project SEED** summer research program provides economically disadvantaged students an internship to experience the studies of a chemist. Students entering junior or senior year in high school work alongside scientist-mentors on research projects, discovering new career paths.
- **Community Outreach** The Institute for Health and Society at MCW consolidates the resources of MCW to provide innovative science education programs for children and adults in the community, employing a multi-disciplinary and inquiry-based approach. Directed by John Meurer, MD, the Institute's unique programs engage students and their parents in the basic process of scientific discovery, to foster curiosity about the natural world and promote scientific literacy through life-long learning. Other community programs include the Upward Bound Math & Science program at the University of Wisconsin-Milwaukee, PEARLS for Teen Girls, Inc., Lead2Change, Milwaukee Area Health Education Center, Milwaukee Public Schools Project Lead the Way STEM curriculum, and MSOE Center for Bio-Molecular Modeling **S**tudents **M**odeling **A R**esearch **T**opic (SMART) Teams. Faculty mentors from the START faculty provide high school students and science teachers in the Milwaukee area high schools with an experience to participate in studies conducted by biomedical scientists.

Undergraduate Students

- **Summer Program for Undergraduate Research (SPUR)** operates in tandem as the next step in the pipeline. The SPUR program is for undergraduates interested in a 10-week program of study leading to the PhD degree in biomedical sciences. Applicants with backgrounds in quantitative disciplines, such as physics, math and computer science and engineering, derive particular benefit from the experience. Diversity is encouraged in the SPUR program, but eligibility is not limited to multicultural or disadvantaged students. Approximately 40 undergraduates participate yearly.
- **MCW Medical and Graduate Student Enrichment Program** Increasing the number of physicians and biomedical scientists who are members of under-represented in medicine (URM) minority groups is vital to ensure that all Americans have access to both culturally competent care and research that addresses disparities. MCW has had success in recruiting URM medical students, but has had less success retaining these students for residency training or for faculty positions. Additionally, the graduate school has had similar difficulties in attracting URM students. One obstacle to retaining our URM medical and graduate students is that many of these students are out of state (non-WI residents), and upon completing their medical or graduate training return to their home states often for family and other support structures. This project identifies highly qualified URM students in the Milwaukee/Southeastern Wisconsin area early in their academic careers, and provide enrichment activities that will enhance the likelihood of choosing a medical/biomedical career, and enrollment at MCW. Specific areas targeted include high schools and undergraduate institutions.

2) Support one year of research training for medical, graduate, and MD-PhD students and MD-fellows in clinical and translational research towards MS or PhD degrees.

- **Graduate Students** PhD in Basic and Translational Science for PhD and MD-PhD students offers in depth training in the basic science plus courses in translational science. It builds on our previous successes in basic research in the areas of biochemistry, biophysics, cell biology, genetics, microbiology, neurosciences, pharmacology, physiology and toxicity to develop translational research training. This program prepares students to carry out research that narrows the gap between current basic science knowledge and clinical practice and to carry out basic science research to answer questions generated at the bedside.
- **Medical Students:** This aspect of the START Program integrates two established medical school strengths: the Medical Student Summer Research Program (MSSRP) and the Physician Scientist Pathway (PSP). The MSSRP directed by Dr. Harder provides 8-11 week medical student research fellowships in the basic, clinical or translational sciences, supervised by MCW investigators. Since 2003, the number of yearly applicants has ranged from 65 – 120 medical students. The ratio of internal vs. NIH funded fellowships is three to one representing a high return on our research training investment. Although the MSSRP is targeted to all medical students enrolled at MCW, approximately 2/3 of each year's multicultural matriculants over the past ten years have participated in the MSSRP, including a number of former students who successfully moved through the pipeline of programs and are now medical students here at MCW. After completing the MSSRP, students optionally can extend this experience as candidates for the **Honors in Research Distinction**, requiring at least 16 weeks of research and the completion of a research thesis. The **Physician Scientist Pathway** (PSP) is a subset of medical students who use protected curriculum time in the M1-M3 years to focus on developing research skills. Dr. Brousseau, who is the PI on this START application, is the director of the PSP for medical students pursuing clinical and translational research with T2 through T4 emphasis. These medical students will have each Thursday to pursue Pathway activities, including course work aimed at a MS in Clinical and Translational Science under the direction of a specific mentor. The majority of medical students completing the Honors in Research are members of the PSP. Those students who excel in the PSP and the MSSRP will be recruited for participation in the START program to further their research careers. They will begin formal coursework in the spring of the M2 year, and the year of research between the M2 and M3 years of medical school training will allow students to complete their research projects and the requirements of an MS in Clinical and Translational Science prior to their Residency. The research initiated during the 2 months between the M1 and M2 years of their medical school experience as well as the dedicated research year will be supported by the START.
- **MD fellows MD subspecialty fellows pursuing clinical and/or translational research will be recruited to participate in the START Program.** These MD fellows, who have already completed medical residencies, will spend 80% of their effort for the last year of training dedicated to pursuing an MS degree and completing their mentored clinical and translational research thesis. A number of MD-fellows currently pursue an MS as part of their training. The START Program provides a more structured research-training program dedicated to

training for research careers. As will be seen below, we continue to mentor fellows who choose to join our faculty and remain part of clinical translational team. While the value of recruiting nationally recognized clinical scientists is apparent we take great pride in retaining some of the best fellows coming out of our programs.

3) <u>Mentor START Program graduates towards successful research careers at MCW</u> Faculty mentoring will continue for START graduates upon completion of their research year. A **Career Development Summary Plan** will be developed for each graduate trainee who continues to train at MCW. The mentoring plan addresses topics related to research and professional development. The goal is to make this an attractive mentoring experience at MCW to retain these highly qualified fellows as the next generation of our physician scientists with careers in clinical and translational research. Career Development Summary for Nicole Lohr, MD, PhD, Assistant Professor of Cardiology at MCW follows:

Career Development Summary for Dr. Nicole Lohr **CAREER DEVELOPMENT SUMMARY** **SUBJECT DOMAIN IN RELATION TO TRAINING OBJECTIVES** **MECHANISMS, RESEARCH AND MENTORS**				
Specific Aims	**Training Objectives**	**Training mechanism**	**Mentors**	**Benchmarks/Timeline**
#1 Measure the effect of electromagnetic energy to stimulate vasodilation in healthy and atherosclerotic vessels	Learn to culture organ arteries, allowing use of siRNA to knockdown NO and cytoglogbin expression. Test effect on vascular dynamics.	Learn siRNA and other molecular silencing strategies to correlate specific molecules to specific vascular functions of PAD.	Dr. Harder is the sponsor and mentor for Dr. Lohr and will coordinate and monitor the training plan in consultation with the other Mentors (below).	Benchmarks will be assessed by selected Mentors; i.e. Harder will cover analytical and genetic mechanisms.
#2 Determine the non-enzymatic source of nitric oxide in endothelial cells exposed to electromagnetic energy	Learn methods to measure reactive nitrogen species and nitrosothiols, allowing MS and related analytical analysis.	Dr. Lohr will learn state of the art techniques for measuring reactive nitrogen species.	Dr. Gutterman is a co-mentor to coordinate studies on vascular biology related to disease for in-vivo experimentation.	Dr. Lohr is currently working with Dr. Gutterman's Lab to enhance her knowledge of vascular wall vascular dynamics.
#3 Determine whether the NO produced after electromagnetic energy exposure can change markers of endothelial dysfunction.	Establish competency in human subject research and proper protocols for obtaining blood and tissue for experimental design.	Gain experience in launching translational research through procurement by learning IRB and human subject related research.	Drs. Jacobs and Raymond will co-mentor Dr. Lohr through clinical and research paradigms towards a career as an academic clinician.	Drs. Jacobs and Raymond will design Dr. Lohr's educational and training program as current and past VA Research ACOS.
Selected course work	**Seminars, workshops and VA learning modules**	**Grand rounds, clinical presentations**	**Clinics and Service**	**Management of clinical and research activities**
1. **Methods in Grant Preparation** teaches grant writing skills with reference to NIH R awards and VA Merit awards. 2**. Advanced Statistical Design** teaches clinical study design, statistical analysis, and experimental protocols.	Dr. Lohr will attend seminars and workshops sponsored by Cardiology and Medicine. She will take all required VA learning modules, and maintain current ethics and ACORP training.	Dr. Lohr will attend National AHA, Amer. College of Cardiology, and Experimental Biology to present her data. Locally, she will attend/give weekly grand rounds.	One half day of echo clinic One half day of general clinic, and one month on general service. A minimum of 75% research time will be protected.	Dr. Lohr will attend quarterly meetings with her mentorship committee. Her progress and productivity will be discussed at these times. The committee will work with Dr. Lohr to find resolve problems coordinating, clinical and research activities

<u>C-2) Objectives and related activities</u> The objectives of the START Program are to train clinicians and health care professionals to conduct clinical and translational research as MDs, PhDs, and MD-PhDs and to attract highly qualified students of diversity to be retained as research orientated faculty at MCW. During the year of research training, students will participate in workshops that teach the skills of grant writing and manuscript writing and other professional development skills, including didactic and small group setting for best practice strategies to optimize communication skills. Graduates of the START Program also will be mentors for successful careers as faculty at MCW.

Activities that will be components of the training program of the START Program include:

- **Organize two-annual school wide conferences on clinical and translational research**. In the fall, organize a research day symposium that includes seminars by the MS and PhD graduates of our START Program, highlighted by a seminar from a keynote investigator. In the spring, organize a poster session day that includes the research of our current trainees and a seminar by an alumnus of the START program. The alumnus also will be the keynote speaker for the START Program graduation ceremony.
- **Provide each member of the START Program a mentored Team Science experience**. Trainees match across professional disciplines in a vertically integrated training experience. Medical students and graduate

students match with an MD-fellow and faculty mentor to address the clinical and translational correlates of their research to predict the next generation of therapies, clinical outcomes, and medical interventions within their patient population. Team Science members will meet our pipelined high-school students and their mentors as participants as role models and mentors.

- Optimize trainee's career development by using an **Individual Development Plan (IDP)** for trainees and graduates of the START Program
- Organize formal workshops to **"Mentor the Mentors"** to guide trainees in fields of study that were not possible or encouraged in earlier times. Mentoring our mentors will promote best practice protocols in training the next generation of clinical and translational research.
- Sensitize the research community at MCW to challenges facing and students of diversity to promote an environment that fosters an "**all inclusive**" atmosphere for scientific discovery.

C-3) Intended Trainees and Training Levels: Medical students, graduate students, and MD-fellows who will complete an MS or PhD degree with an emphasis in clinical and translational research are the intended trainees of the START Program. Medical students will be selected primarily from the T2-T4 Physician Scientist Pathway after completion of the Medical Student Summer Research Program. Graduate and MSTP students will be selected based upon their interest to extend their dissertation research to have a translational focus. MD-fellows who are in the MS in Clinical and Translational Science Program that is designed for MD fellows who wish to pursue a medical career with a research focus, comprise a unique subset of fellows who complete the MS after residency training.

C-4) Required academic and research background needed to pursue training: The trainees entering the START program will be solidly grounded in basic courses, including science, math, and humanities. Our medical school, graduate students, and MD-PhD students have a broad range of undergraduate emphasis, and each student has completed a set of required undergraduate courses. Students with strong quantitative backgrounds (engineering, mathematics, chemistry, and physics) will be especially encouraged to enter the START Program, since we anticipate that these students will develop new technologies to address new advanced in clinical medicine. We anticipate that our trainees will be prepared to complete the MS and PhD curricula as outlined in sections 6 and 7 below. When appropriate, we will use a holistic approach to identify those candidates with highest potential to become academic physician-scientist who have a passion of biomedical research.

C-5) Plans to accommodate differences in preparation among divergent trainee groups: All trainees will need to register in the Graduate School at MCW to take courses towards the MS and PhD degree. Upon entry into our graduate school and/or medical school, applicants will apply for entry into the START Program through existing application processes. Candidates will be interviewed and their transcripts assessed for deficiencies in their undergraduate portfolio that can be resolved through course work within the CTSI affiliated institutions. MCW and our affiliated CTSI undergraduate schools have agreements for such situations. In addition to course work, some students may require specific mentoring during their graduate school or medical school training, which will be facilitated by an Internal Advisory Group selected from the list of participating preceptors. In addition, senior MD-PhD trainees are effective tutors.

C-6) Increasing Workforce Diversity: In addition to the MCW pipeline programs, the START Program will leverage our CTSI affiliate, Marquette University's Health Career Opportunity Program (HCOP) which has been awarded a 3-year, $1.6 million renewal from the Health Resource Service Administration (HRSA) for its nationally recognized recruitment and retention program for disadvantaged students. This federal program is designed to reduce health care disparities in under-served areas by graduating health professionals that are more likely to return to serve disadvantaged segments of the population. The Marquette HCOP offers programming to disadvantaged students interested in physical therapy, dentistry, physician assistant studies, biomedical sciences, clinical laboratory science, and speech pathology and audiology.

C-7) Core Competency Curriculum: An objective of the START Program is to mentor highly qualified students of diversity into careers as MDs, PhDs, and MD-PhDs who conduct research in clinical and translation research towards the MS and PhD degrees. MCW is dedicated to the recruitment, admission, retention and graduation of talented applicants from diverse backgrounds and underrepresented in the biomedical workforce. MCW identifies these groups as African-Americans, mainland Puerto Ricans, Mexican-Americans, Native Americans, and Alaskan and Hawaiians. The START Program works with the Office of Student

Affairs/Diversity to achieve MCW's Diversity policy. These criteria include students from low economic backgrounds or from schools with low resources, as well as students for which English is not their primary language. The MD-PhD Program coordinates diversity recruitment and retention activities through the medical school's Office of Student Affairs Diversity, in conjunction with its Associate Dean, Dawn Bragg, PhD. Diversity recruitment utilizes several recruitment strategies to recruit and retain a diverse student population.

Medical student-MS curriculum Scholarly Pathways are a required component of the medical school curriculum for all First and Second Year students and is optional in the Third Year. The Physician Scientist Pathway (PSP) allows students to individualize their medical training, exploring a research career path of interest. PSP trainees work with peers and faculty, building on the foundation of medical school experiences to pursue an area of common interest in greater depth. Physician-Scientist Pathway M1-M2 year includes a **structured curriculum** composed of a core set of competencies delivered through monthly workshops, or core sessions and an **experiential non-core research activity** guided by a faculty advisor to apply core concepts in clinical and translational and bench to bedside research. During the M3 year, medical students complete and present the scholarly project. Dr. Brousseau and Dr. Harder, Director and Associate Director of the START Program, have reported that many students integrate their pathway work with the MSSRP described above to allow more formal research time. The integration of these programs will be the foundation for an MD-MS where medical students take a year of research between the M2-M3 years of medical school training. A typical MS in Clinical and Translational Science (MD-MS) curriculum for a medical student in the START Program follows:

Medical Student -MS in Clinical and Translational Science (MD-MS) in START Program	
Medical Year 1 – Physician Scientist pathway	• Med CITI - Ethics & Integrity in Science, 1 cr.
Summer between M1 and M2 year	• Medical Student Summer Research Program
Medical Year 2	• Clinical and Translational Science seminar 0.5 cr Elective 3 cr
Research Year (START supported) • All graduate courses are offered Thursday afternoons. • Courses listed will be spread over the entire twelve month period	• Clin. Trial Design, 1 cr. • Biostatistics I (3 cr) and Biostatistics II (3 cr) • Intro to CTS, 1 cr. • Intro to Epidemiology, 3 cr. • Research Methods in Epidemiology, 3 cr. • Readings and Research (6 cr)
Medical Year 3 • Med Research Elective	• Clinical and Translational Science seminar 0.5 cr • Master's Thesis, 3 cr.

MD fellow-MS Curriculum MD fellows may pursue an MS in Clinical and Translational Science. The START program will draw from the pool of subspecialty fellows with an interest in clinical and translational research. These subspecialty fellowships predominantly start with an intensive clinical year, followed by more protected time for research in the 2nd and 3rd years. We will take the opportunity provided by those latter two years to recruit selected Fellows for the START program. They will focus on introductory coursework during their 2nd year of fellowship and be supported with 80% research time and the completion of an MS in Clinical and Translational Science during their third year. The coursework and research efforts for the MD-Fellows follows the same general outline described above for the MD-MS medical students. A typical MD-fellow follows:

MD fellow-MS in Clinical and Translational Science (MD-MS) Curriculum	
Fellowship year 2 (Fall) • Introduction to Epidemiology, 3 cr • Clinical Research Methods Workshop, 1 cr • Introduction to CTSI, 1 cr • Seminar, 0.5 cr;	**Fellowship year 2 (Spring)** • Research Methods in Epidemiology, 3 cr • Med CITI - Ethics & Integrity in Science, 1 cr • Readings and Research, 3 cr • Seminar 0.5 cr
Fellowship year 3 (START Supported) • Thesis Research 6 cr • Introduction to Biostatistics I, 3 cr • Advanced Biostatistics, 3 cr • Clin. Trial Design, 1 cr • Readings and Research (6 cr) • Seminar, 1 cr	

Graduate Student in the PhD in Basic and Translational Science (PhD and MD-PhD) Graduate students matriculate into existing doctoral programs: Biomedical Sciences, Neuroscience, Biophysics Imaging, Pharmacology and Physiology. During their first year of studies they chose a mentor in the PhD in Basic and Translational Science Program when they also apply to participate in the Basic Science Department and Basic and Translational Science Program. During their studies these studies have 6 Credits of Department and 6 credits of Translational course work to complete. Throughout the program, students participate in monthly non-credit program seminar. The students incorporate one translational dissertation specific aim at may include a) Investigations to discover the pathobiologic basis of human disease and directed towards the invention or improvement of diagnostic, prognostic or therapeutic strategies, b) characterization of the biological effects of therapeutics, c) biomarker discovery and validation, or d) drug, diagnostic tool or medical devise development. Students complete an Individual Translational and Clinical Training Plan and have 4 clinical experiences per year in years 3-5 of their graduate training. These students are mentored by basic- and clinical- scientists. A typical PhD in Basic and Translational Science (PhD and MD-PhD) curriculum follows:

Curriculum PhD in Basic and Translational Science (PhD and MD-PhD)	
Graduate Year 1 • Standard Entrance Graduate Curriculum • Choose Dissertation Advisor • Apply to PhD in Basic & Translational Science Program	**Graduate Year 3** • Boundaries of Science and Medical Practice • Pathophysiology Course (1-3 cr) • Translational Science Course (1-3 cr) • Translational Science seminar (audit) • Continue Dissertation Research
Graduate Year 2 • Standard and Departmental Graduate Curriculum (6 cr) / Qualifying Exam • Biostatistics (1 or 3 cr) • Initiate Dissertation Research	**Graduate Year 4** • **Dissertation Research (START supported)** • Translational Science Seminar (non-cr) • Seminar in Basic and Translational Science • Defend Dissertation

Students will enroll in one of the two medical anthropology courses **Applied Medical Anthropology** and **Health Delivery or Ethnomedical Systems and Health Care Sectors**. Medical anthropology courses will train the next generation of culturally-competent Clinical and Translational Science Researchers by applying medical anthropological theory and practice to real world settings. Students will understand the relevance of the social science theory and learning for research practice. Each course will provide an introduction to diverse aspects of the field of medical anthropology by focusing on theoretical questions of how one frames "illness," "health," "healing" or "medicine" as an object of study. Specifically, the course: Applied Medical Anthropology and Health Delivery, examines the intersections of social science theory of culture and medicine. The course will examine illness, healing and medicine in a social, cultural and historical context. Students will develop critical questions concerning some of the ways that the concept of "culture" is used within medical research and health delivery. While the course: Ethnomedical Systems and Health Care Sectors, focuses on ethnomedical systems and beliefs of various ethnic and racial minorities in the United States. Using case studies of illness narratives, the course will examine current medical practice and research in the United States alongside issues of health disparities and structural violence.

C-8) Promotion of best practices in research, how to avoid bias in experimental design and reporting:
There is a probability that trainees from diverse backgrounds will train in the START program with some degree of internal bias related to expectations and experiences one of the required START courses discuss research ethics. This course will address how to develop a hypothesis devoid of pre-conceived bias, and proper reporting of research and literature data. Accompanying this course will be a weekly journal club discussing topical and controversial data reporting and landmark manuscripts, which had to be retracted for targeted reasons. In addition, these journal club topics will discuss the importance of honest data reporting and interpretation will be discussed including plagiarism, multiple use of similar or identical data, and other topics common to problems in communications.

C-9) Describe individual development plans, and plan implementation, including team science and problem solving. The MSTP uses an Individual Development Plan (IDP) to assess the development of our trainees. This IDP allows the trainees to self-assess achievement during the prior year and their goals for the coming year. There are three versions of the IDP for the three stages of training, M1/M2, Graduate Years, and M3/M4. This IDP will be used for the MD-MS trainees and modified for the MD-fellows to address the fellows more advanced careers goals. The IDP is completed annually by the trainees in August and reviewed by the Leadership Committee and is used for talking points during the annual one on one meeting with trainees. **The IDP is in the appendix (Appendix #3)**. During the research year supported by the START Program, each

student will participate in a mentored Team Science experience. Students will match across professional disciplines in a vertically integrated training experience. Medical students and graduate students match with an MD-fellow and faculty mentor to address the clinical and translational correlates of their research to predict the next generation of therapies, clinical outcomes, and medical interventions within their patient population. Team Science members will also include pipelined high-school students and their mentors as participants.

Examples of individual trainee programs: Responsibility for daily supervision of trainees is delegated by the Program Director (Dr. David Brousseau) to each faculty research preceptor. Preceptors are charged with helping trainees develop a sound understanding of the research problem under investigation, providing guidance in experimental design, analytical methodology and data collection, analysis and interpretation, and providing a research experience, which is supportive of the professional goals of the trainee for developing a solid foundation for future careers involving research.

C-10) Describe how flexibility to adapt to trainees needs will be provided: A representative example of adaptation to trainee needs will be by providing medical students, fellows, and health science professionals all ending with an MS in Clinical and Translational Science we are meeting the needs of our target group, including minority trainees.

C-11) To promote collaboration through team science: **Team science** is at the pinnacle of the CTSI. By bringing together our regional partners, we will ultimately have a greater impact than working alone. With an emphasis on serving our under represented communities working with UWM, Marquette University, will greatly expand this goal. Along with MCW these institutions in particular have as part of their mission outreach programs aimed at the underserved populations in Milwaukee, especially with respect to health care workers in Nursing, Physical therapy, and most recently the Stroke Rehabilitation Center along with MCW. Additionally, the Veterans Hospital and Medical Center has a longstanding program in neural-trauma and rehabilitation. MCW, especially with Physical Medicine and Rehabilitation, has developed a long-standing partnership in reaching out to underserved veterans. Such team science approaches to translational research is at the heart of the CSTI mission and reflected in our training missions such as this START. **During the research year supported by the START, each student in the Program will participate in a mentored Team Science experience.** Students will match across professional disciplines in a vertically integrated training experience. Medical students and graduate students match with an MD-fellow and faculty mentor to address the clinical and translational correlates of their research to predict the next generation of therapies, clinical outcomes, and medical interventions within their patient population. Team Science members will also include a pipelined high-school students and their mentors as participants in the program.

C-12) Support a range of disciplines including informatics and biostatistics: In addition to the traditional "basic science" directed PhD Programs, students may pursue a PhD in Biophysics, Biostatistics, Neuroscience, Pharmacology and Toxicology, and Public and Community Health. MCW, along with its CTSI partnering institutions, has adopted a multi-departmental center based mechanism supporting the primary research missions of the institution. These multi-departmental centers, include a nationally recognized Cardiovascular Center (CVC), the Cancer Center of South Eastern Wisconsin, the Human Molecular and Genomics Center (HMGC) with a focus on Personalized Medicine, and the Neuroscience Center. These centers extend the research possibilities medical and graduate students to pursue MS and PhD degrees.

C-13) Develop unique and transformative training experiences that cross traditional boundaries: The START Program goes beyond a clinical and translational research program. The program will provide trainees, including those from under represented ethnic backgrounds, new tools such that at the end of this program MDs and PhDs can conduct population based, outcome centric, projects, which have an impact on health problems and disparities. We will use newly developed didactic course work imbedded in Medical Anthropology and Cultural Diversity enabling our trainees to begin to understand the barriers which prevent development of translational outcomes to solve community health care issues. Trainees entering this program will gain core competencies enabling clinician scientists and health care providers to design meaningful translational studies. Graduates of the START Program will be able to: design clinical and translational research (including population based trials), understand how to critique literature, implement outcomes based research protocols, understand statistical analysis and biomedical informatics, write research reports and manuscripts, understand cultural diversity and community engagement, experience team based science,

design studies across specific disciplines, and lead research groups. This knowledge will have a strong impact of breaking cultural barriers.

C-14) Describe plans to collaborate with other hubs: The START Program is a multidisciplinary clinical, translational, research-training program similar in purpose to traditional NIH T32 training grants. There will be a strong focus on working with local university partners and regional CTSI hubs (refer to the MARCH) initiative described in the CTSA grant narrative. We will use as an example of the collaborative nature of this program; the newly developed South East Regional Stroke and CNS Injury Rehabilitation Center. This Program is centered at MCW in the Dept. of Physical Medicine and Rehabilitation (PM&R). Our closest community partner is Marquette University where much of the basic bioengineering and physical therapy research is done. PM&R has two fellows working at least two days/week at Marquette to comprise the clinical translational hub. Similarly, Marquette sends health care professionals, usually physical therapists, biomedical engineers and exercise physiologists to MCW to complete the full translational hub of the program. In addition to Marquette University, Nurses and biomedical engineers from UWM come to both MCW and Marquette University to participate and add expertise to the program. We are currently engaging the University of Wisconsin-Madison (UW) to work with us as a regional hub. UW is a NIH designated Stroke Center, and we will contract for the rehabilitation portion of the Stroke Center.

D TRAINING PROGRAM EVALUATION Several mechanisms have been established within the START Program to chart trainees' progress and mentor's effectiveness.

D-1a Engages faculty, staff, trainee's in education efforts and obtain their feedback to identify weaknesses and suggest improvements Anonymous Evaluation Survey Each year, current START trainees, faculty mentors, and staff will complete an anonymous evaluation, scoring programmatic activities and personnel. The outcomes identify activities that had a positive impact for our trainees and those that did not. The outcome is shared with the START leadership and the Trainee-Mentor Evaluation Committee. The Anonymous Evaluation Survey is included in appendix **(Appendix #4).**

D-1b Track trainee career progress The **Individual Development Plan (IDP)** provides the START Program with the trainee's perceptions of their progress in the program, how the program has helped them achieve their goals, and what the program can do to facilitate their goals. A similar IDP used by the MSTP for the past 3 years and has proved valuable to plot the progress of our trainees and to identify specific needs and challenges of individual trainees. Trainees will complete the IDP annually prior to their one-on-one meetings with the Program Director. Topics asked are stage specific. The IDP form is in the appendix **(Appendix #3)**.

Plan for tracking trainee career progress newsletter Alumni Evaluation and Participation The director sends a personalized letter to each alumnus in their first year upon graduating from the START program. This letter asks our alumni how well the research year supported by our START Program prepared them for careers as clinical and translational scientists. START graduates are a unique resource in program evaluation, providing a perspective on how our program prepared them for their careers as physician scientists; one ultimate success of our START Program. The CTSI mails a bi-annual *CTSI Newsletter* that will include updates on the professional status and activities of our START alumni. This will maintain contact with START alumni. These contacts also link alumni with current trainees who are perusing similar career paths or are located at an institution where our trainees might be considering a career. Alumni will be invited to return to the START program as guest speakers to give of career development activities.

D-1c Identify program performance assessment tools to evaluate curriculum, mentors, research training opportunities, trainees.

- **Annual mentor evaluation document** Mentors complete a six-month and end of year evaluation of the trainee's research progress and professional development. The document is shared by this committee and members of the START Leadership Committee. Students anonymously evaluate each of the formal courses within their curriculum, which is reviewed by the Graduate School of Biomedical Sciences and provide to the Course directors and graduate school. Courses are evaluated annually by the graduate school. Mentors provide an annual assessment of their student's progress. This document is counter signed by the student and reviewed by the graduate school.
- **Mentor-Mentee Evaluation Committee** Each year, current START trainees will complete an anonymous evaluation, scoring programmatic activities and personnel. The outcomes identify activities that had a positive

impact for our trainees and those that our trainees felt were not effective. The outcome is shared with the START leadership, the Associate Program Directors, and the Trainee-Mentor Evaluation Committee. The Anonymous Trainee Evaluation Survey is included in the appendix (**Appendix #4**)**.**

- **PhD qualifying examination committee** Trainees studying for the PhD degree must pass a qualifying examination during the second year of graduate studies. The examination is standardized by the Graduate School of Biological Sciences and the committee members are experiences examiners who assess didactic knowledge as well as integrative skills and creativity. This committee either approves or disapproves the trainee's projected capacity to completion PhD quality research.
- **MS Thesis and PhD Dissertation Committee** The research progress of START trainees are monitored by an MS thesis or PhD dissertation committee. Committee members include faculty from the mentors department and faculty members for other departments. In addition, PhD dissertation committees include an external reviewer from an outside institution. These committee either approve or disapprove the research conducted is of the quality expected of the degree granted.
- **CTSI directed Evaluations** Universally accepted metrics for career success across CTSAs typically fall in two domains – intrinsic (e.g., motivation, leadership skills, etc.) and extrinsic career success factors[15.] In 2012, CTSI implemented an online tracking tool developed by the Rockefeller Univ. CTSA, called the Graduate Tracking Survey System (GTSS). The GTSS captures individual-level data and scientific or medical paradigm changing discoveries. Short-term success is defined as completion of the MD and PhD degrees. The CTSI will also utilize the Clinical Research Appraisal Inventory (CRAI)[15-17]. Trainee evaluation will capture more immediate indicators of program success, including training-program relevance to one's career path, and research self-efficacy. Trainees will complete the CRAI at entry into the program and again at the end of his/her time in the program. We will utilize a shortened version of the CRAI, as the 12-item CRAI is faster and less burdensome to complete, while retaining strong psychometric properties of the original CRAI [18].

D-1d Show evidence that CTSA supported activities are synergistic (not duplicative) with other funded NIH T32 programs. Table 3 shows that none of the active T32 grants have a goal to support clinical and translational research as a component of an MS or PhD degree.

E. Trainee Candidates

E-1 Applicant pool Table 8a shows the 2012-2013 Pre-doctoral Applicant Pool for the **Medical Student Summer Research Program** and the **MSTP**. The Medical Student Summer Research Program included **121** applicants who had an average MCAT of 33 and a 3.69 GPA. The MSTP included **163** applications had an average MCAT of 32-Q and GPA of 3.56. The MSTP Training Grant Eligible applicants to matriculants ratio was 22.8:1, about the average for an MSTP program.**CALIBER OF CURRENT TRAINEES** The qualifications of the current trainees associated with our medical student in the **Physician Scientist Pathway** and the MD-PhD students in the **MSTP** are shown in **Table 9A.** The 61 current **Physician Scientist Pathway** medical student trainees have a combined average MCAT of 32-R and an average GPA of 3.73, which exceeded our expectations for quality, and overall satisfaction of the Physician Scientist Pathway within the program. The 7 MD-fellows who graduated in 2013 with a MS in Clinical and Translational Sciences are shown below, faculty are CTSI faculty and listed in the main renewal.

Profile of 2013 graduating MD-MS Fellows		
MD-fellow	**Mentor**	**Thesis Title**
Muhammad Ali, MD	K. Sacian, MD	Acute Kidney Injury and its effect on mortality among hospitalized Patients with Cirrhosis
Thomas Aufderheide, MD	E. Brooke Lerner, PhD	Ventilation Rate and use of the Impedance Threshold Device are Correlated with Hemodynamics during CPR in humans
Chelsea Collins, MD	Mary Eapen, MBBS, DCH, MRCPI, MS	Long-term Survival and Late Deaths following Unrelated Donor Transplantation on Children and adolescents with Acute Leukemia
Garick Hill, MD	Jane M. Kotchen, MD, MPH	Feeding Dysfunction in Single Ventricle Heart Disease
Elizabeth Kessler, MD	James Verbsky, MD, PhD	Longitudinal Analysis of Lymphocyte Subset Distribution and Cytotoxic Molecule Expression in Patients with Juvenile Idiopathic Arthritis
Yachiyo Kuwatsuka, MD, PhD	Mary Eapen, MBBS, DCH, MRCPI, MS	Graft-versus-host Disease Rate and Survival After Cord Blood Transplantation and Acute Leukemia
Andrea Morrison, MD	David Brousseau, MD, MS	Caregiver Low Health Literacy is Associated with Non-Urgent Emergency Department Visits for Fever

The 42 current **MSTP** trainees have a combined average MCAT of 35-Q and an average GPA 3.78 and have graduated from research-intensive undergraduate institutions. Over the past 10 years, 25-trainees have graduated with MD-PhD degrees from our MSTP. Over this period, the average time to graduation was **7.6** years, the total average number of first authored PubMed referenced publications was **2.9;** the total average number of internal authored PubMed publications was 5.4 **Table 6.** The 15 PhD and MD-PhD Students in PhD Program in Basic and Translational Sciences MD-fellows who entered the program between 2011-2014 are shown below, faculty are members of the Graduate Faculty.

E-2 Nomination, selection and reappointment process Nominations, candidates will apply to the START Program through existing application mechanisms in the CTSI for MD-MS applicants and the Graduate School for PhD and MD-PhD applicants. The START Program Admission Committee will oversee student recruitment. The committee will comprise the participating leadership of the START Program and several members of the CTSI faculty. Dr. Brousseau will be the Chair of the admissions committee. **Selection,** Applicants will be ranked based upon their didactic scores, research proposal, and their progress during their summer research between the M1-M2 years (M1-M2) or progress made during the early years of their PhD training (PhD and MD-PhD). The application packet will also include a Trainee's Research Plan written by the mentor. Applications will be accepted between August 1st and December 1st for the start of the research year in July. Applicant credentials will be reviewed from September to December and the Admission Committee will interview applicants. Between January and February, acceptances will be made. The acceptance will be extended for 20 days to allow the trainee and the mentor to confirm their interest in Program. Upon acceptance, medical school students will request a leave of absence from the Medical School. Candidates will interview with two members of the START leadership, one CTSI faculty and a current START student. The interview evaluation sheet is included in the appendix (**Appendix #5)**. We anticipate interviewing 20 students to fill the 10 training slots in the START. **Reappointments,** the Admission Committee will consider a student's request for a reappointment based upon a having had a successful year's research that needs further investigation to complete a publication or pursuing a new approach to clarity points in the study, for example. In this situation, a formal request for reappointment would be made by the trainee and co-signed by the mentor. Prior to approving a request for reappointment, the trainees would interview with the Admission's Committee, giving a formal research seminar and defending their reappointment application.

F. Institutional Environment and Commitment to Training

F-1 Training environment MCW is a private, freestanding academic medical center dedicated to leadership and excellence in patient care, research, education, and community service, offering MD, PhD, MS, MPH, and MA degrees. MCW employs more than 1,500 full-time and part-time faculty, in addition to more than 3,400 full-time staff, 200 part-time staff and 240 project and limited-term employees. MCW faculty members supervise approximately 650 physicians in residency training and 200 physicians in fellowship training throughout the MCW Affiliated Hospitals. There are more than 1,200 students enrolled in educational programs at MCW, including 820 medical students and more than 400 graduate students. MCW Libraries comprise three facilities: the main research library located in the Health Research Center; and two clinical libraries, one in Children's

Profile of PhD and MD-PhD Students in PhD Program in Basic / Translational Sciences (2011-2014)

BTS Program	Student	Mentors	Clinical Advisor	Dissertation Topic
2014 Cell Biology	Kathryn Hendee	E Semina, PhD	NA	PITX transcription factor family involvement in human ocular diseases
2014 Biochemistry	Matthew Waas	R Gundry, PhD	N	Biomarkers on cardiomyocytes for transplantation
2014 Physiology	Anna Williams	Z Bosnjak, PhD	NA	Effects of isoflurane and glucolipotoxicity on NO signaling.
2014 Microbiology	Cheng-Yin Yuan	W Drobyski, MD	NA	Prevention and attenuation of the pathology of Graft vs Host Disease
2013 Pharmacology	Johnathan Ebben	M You, MD, PhD	NA	Development of peptide based vaccines to prevention and treatment recurrence of non-small cell lung cancer
2013 Physiology	Thomas Langer	B Forster, PhD	K Marcdante, MD	Determination of the causes of respiratory depression with opiates following anesthesia
2013 Physiology	Shaun Rasmusen	A Geurts, PhD	NA	Determination of ways to prevent liver damage in Tyrosinemia type I
2013 Physiology	Britany Wade	D Mattson, PhD	NA	Role of T-cells in hypertension
2012 Physiology	Maria Angeles	M Liang, PhD	NA	Role of microRNA in hypertension
2012 Pharmacology	Brett Deml	E Semina, PhD	D Bick, MD	Identification of new genes that contribute to congenital ocular disease
2012 Microbiology	Allison Reeme	R Robinson, PhD	M Bielke, MD	Determining the susceptibility and severity of Mycobacterium tuberculosis infection
2012 Pharmacology	Mike Tanner	M Widlansky, MD, MPH	M Windlansky, MD	Endothelium dysfunction during hypoglycemic states of Type II diabetes patients
2011 Physiology	Nathan Rudemiler	D Mattson, PhD	E Cohen, PhD	Effects of the immune system on renal damage and in hypertension
2011 Biochemistry	Zachary Shaheen	J Corbett, PhD	C Williams, MD, PhD	Insulin signaling and the activation, survival and proliferation of macrophages
2011 Cell Biology	Andy Weyer	C Stucky, PhD	Q Hogan, PhD	Echanotransduction related to chronic pain conditions in patients with cutaneous mechanical hyperalgesia

Hospital of Wisconsin and one in Froedtert Hospital. The libraries hold among the largest health sciences collections in the Midwest, with more than 250,000 volumes, 3,000 journals, 800 electronic books, and 85

databases. Approximately 200 scientists are engaged in postdoctoral research fellowship training through the Office of Postdoctoral Education. *Science Magazine* consistently ranks MCW among the top 20 Best Places to Work for Post docs based on our exceptional training and mentoring. MCW provides continuing medical education to more than 15,000 health professional registrants each year. The MCW Center for Science Education also provides educational programs for approximately 7,000 students, teachers, and adults annually. MCW stands as the academic center of the Milwaukee Regional Medical Center, which houses our teaching partners: Froedtert Memorial Lutheran Hospital (FMLH), Children's Hospital of Wisconsin (CHW), the Milwaukee County Mental Health Complex (MCMHC), Curative Rehabilitation Center (CRC), and the Blood Research Institute of the Blood Center of Southeastern Wisconsin (BRI). MCW is a major national research center and is the largest research institution in eastern Wisconsin. In FY2014, faculty received more than $154 million in external support for research, teaching, and related purposes, of which more than $138 million was allocated for research ($79.5 million from NIH). MCW is the largest research institution in the Milwaukee metro area and the second largest in Wisconsin. MCW is particularly distinguished for excellence in cardiovascular disease, genetics, cancer, imaging, bone marrow and kidney transplant, and pediatrics. In 2013, MCW has advanced in all areas of research, including translational sciences, clinical trials, and in the T3-T4 research arenas. Additionally, the College has 220 pending and issued patents, and has research and development affiliations with other major universities and research institutions, as well as government and venture capitals groups. The College has launched 18 start-up companies and licensed technologies to more than 50 pharmaceutical, diagnostic, biotechnology, and medical device corporations. This environment is exceptional for the integration of student training with respect to clinical and translational research.

F-2 New areas of recruitment leveraging faculty expertise The START Program will leverage faculty expertise to direct studies in order to expand the training possibilities in contemporary areas of biomedical research. The KERK and MU PhD Clinical and Translational Rehabilitation Health Science will be briefly described as areas of research that will be incorporated for sites where students the START Program can pursue the MS and PhD in clinical and translational science within the first two years of TL1 funding.

- **Clinical Genome Wide Sequencing Core for the Undiagnosed Disease Network** This program (HG007943-01) focuses on creation of a sequencing core for the Undiagnosed Disease Program (UDP) as well as comparison of the utility of genome-wide sequencing (GWS; also known as whole genome sequencing) versus Whole Exome Sequencing (WES) for the identification of causal variants. This program utilizes functional GWS at MCW and Illumina to compare GWS and WES for diagnostic success. This program will conduct GWS for all participants enrolled in the UDP creating the opportunity to compare utility of WES versus GWS. Students will be integrated into innovative lab and bioinformatics teams to test the hypothesis that GWS will produce at least 25% more diagnoses than WES. Students will: generate clinical grade GWS for all UDP cases sequenced and perform read mapping and variant calling, will undertake clinical grade tertiary analysis of the data using our clinically validated analysis platform and provide clinical interpretation and report generation for all cases requested; and confirm the NextGen sequencing results using Sanger techniques. MS and PhD students will be involved with basic scientists and clinical scientists for laboratory operations and methodologies. This program places students into a team as a sequencing core to determine if GWS or WES can provide a diagnostic advantage for undiagnosed human disease.

- **Graduate Studies for the PhD in Clinical and Translational Rehabilitation Health Science at Marquette University** Marquette University graduate program in Clinical and Translational Rehabilitation Health Science develops clinical and translational leaders to better the lives of those who suffer from human function disabilities. The doctoral program builds upon a student's clinical degree and expertise with rigorous training in translational research, The Program place a unique emphasis on various rehabilitation disciplines, including pathokinesiology, neuroscience, motor control, exercise physiology, sports medicine and community wellness. A typical curriculum for a PhD in Clinical and Translational Rehabilitation Health Science at Marquette University follows:

Curriculum PhD in Clinical and Translational Rehabilitation Science at Marquette U	
Graduate Year 1-3 • rehabilitation systems physiology • applied neurophysiology • statistics	 • molecular genetics • research methodology • advanced electives
Translation research (START Supported)	
• Departmental seminars	• Dissertation Defense

F-3 Recruitment plan and how it will be implemented The START Program will leverage the current efforts of the MSTP Program and the Medical School to implement a local and national efforts to recruit students of diverse backgrounds into the START Program. The START Program will combine efforts that include career workshops given by Dr. Barbieri to the high school and undergraduate pipeline programs at MCW and recruitment activities by the Medical School and the MSTP to recruit URM students through visits to colleges/universities and recruitment fairs. Recruitment activities focus on recruitment fairs to maximize efforts to reach the largest pool of students. Typical recruitment venues include:

- University of Illinois, IL
- Minority Student Recruitment Fair, U of Missouri,
- GSA (Group Student Affairs), Ohio
- Minority Health Science Recruitment Fair, UC-Davis
- University of Minnesota-Minneapolis Graduate Fair
- Northern Illinois University Graduate Fair
- Ohio State University Graduate Fair
- Minority Health Sciences Recruitment Fair, CO
- Stanford University Minority Medical Alliance, CA
- Student National Medical Association, Atlanta, CA
- National Hispanic Medical Association, DC
- Minority Health Sciences, U of Puerto Rico
- Minority Student Recruitment Fair, MD
- Student National Med Assoc Recruitment Fair, MN
- Minority Health Sciences Recruitment, CA

The Program Director of the MSTP recruits at,

- Annual Biomedical Research Conference for Minority Students (ABRCMS)
- Society for Advancement of Chicanos and Native Americans in Science (SACNAS)

F-4 Sufficient protected time for project lead and other faculty to contribute to training Faculty times are incorporated into the budget as described in the application instructions.

F-5 Synergy with Other Programs The START Program has intrinsic synergy with the Physician-Scientist Pathway in the Medical School, the MSTP, and the MD-MS and PhD in Clinical and Translational Science Programs within the Graduate School. We anticipate that the START trainees will foster expanded synergy in these training programs by integrating not only for students supported by the START Program, but also with their contemporaries within their parent programs who share similar careers goals. For example, Marquette University's Health Career Opportunity Program (HCOP) was awarded a 3-year, $1.6 million renewal from the Health Resource Service Administration (HRSA) for its nationally recognized recruitment and retention program for disadvantaged students. This program is designed to reduce health care disparities in under-served areas by graduating health professionals that are more likely to return to serve disadvantaged segments of the population. The Marquette HCOP offers programming to disadvantaged students interested in physical therapy, dentistry, physician assistant studies, biomedical sciences, clinical laboratory science, and speech pathology and audiology.

F-6 The Minority Pipeline for Graduate Program The Marquette HCOP is one of the nation's longest running, continuously funded programs of its kind in the country, having educated more than 700 health care professionals from disadvantaged backgrounds. HCOP offers several exciting career exploration programs for high school and middle school students from disadvantaged backgrounds.

II PROGRAM PLAN

The overall goal of the mentored clinical translational research training program is to facilitate the research career development of early-stage clinical/translational investigators.

A. PROGRAM ADMINISTRATION

Leadership

Theodore Kotchen, MD, is Director of the KL2 program. He is Professor Emeritus and Associate Dean for Clinical Research at the Medical College of Wisconsin. He is an endocrinologist with longstanding involvement in research and patient care related to hypertension. Primarily funded by NIH, his research interests relate to the regulation of arterial pressure, nutrition and blood pressure, mechanisms of hypertension, and genetic contributions to hypertension. An underlying strategy of his research has been translation of laboratory science into the clinical arena. He has served on a number of NIH review groups, and from 1986-1988 he chaired the Experimental Cardiovascular Sciences study section. He has also served as a consultant to the Center for Scientific Review (CSR) at NIH. In that capacity, he assisted in evaluating the outcomes of NIH peer review of clinical research. He has been a member of several editorial boards and has served as Guest Editor for Hypertension and Section Editor for Current Hypertension Reports. He is currently co-Executive Editor of the American Journal of Hypertension.

Related to his own research, Dr. Kotchen has mentored more than 15 post-doctoral trainees, most of whom hold faculty positions. Within the CTSI, he has been an active faculty member of the Clinical Research Scholars Program (formerly K30) for more than 10 years, and he has been Director of the Clinical Research Training Program since its inception in 2000. In these capacities he regularly meets with trainees in both programs, both individually and in group sessions. During these sessions, he leads discussions in which trainees critique drafts of each other's manuscripts and grant applications. In addition, these discussions frequently focus on issues related to barriers and opportunities for career development. Currently, Dr. Kotchen meets every other week for 1-2 hours with the current group of Clinical Research Training Program trainees. He also meets with them 2-3 times per year on an individual basis to review their progress and career development plans. He provides semi-annual progress reports for each trainee to the Director and the Executive Committee of the CTSI.

Jane Morley Kotchen, MD, MPH, Professor of Medicine at MCW, is Associate Director of the Program. Her research focus is in epidemiology. She has a long history of NIH-funded research, including a community-based project of High Blood Pressure in the Young, and community-based hypertension control projects in rural Kentucky and in Chicago/Milwaukee. She is the site Principal Investigator for the long standing NIH Women's Health Initiative. She also serves as the Principal Investigator for a 5-year community-based research project focused on cardiovascular risk reduction in a rural Wisconsin county. She serves as Director of the CTSI Master of Science in Clinical and Translational Science Program, which provides clinical research training for both pre-doctoral and post-doctoral students. In addition, since its inception in 1999, she has served as the Director of the CTSI Clinical Research Scholars Program (formerly K30), a two-year research career development program for junior faculty, which also provides research training for the CTSI KL2 Scholars. Dr. Kotchen has been a reviewer for both the NHLBI K23 and K08 clinical research career development grant applications.

Committees

Applicant Review Committee. As in the past, with each round of competition, applications will be reviewed by a multidisciplinary group of clinical/translational investigators drawn from the 4 academic partners of the CTSI. The composition of the current committee is as follows: *Kristina Ropella, PhD*—chair (former Professor and Chair, Dept of Biomedical Engineering at Marquette, current Interim Dean of College of Engineering at Marquette; *Joshua Fields, MD* (Assistant Professor of Medicine at MCW and Associate Medical Director of the Blood Center of Wisconsin); *Ron Gerrits*, *PhD* (Associate Professor of Electrical Engineering & Computer Science, MSOE); *Elizabeth Jacobs, MD* (Professor of Medicine, MCW and Associate Chief of Staff for

Research at the Clement Zablocki VA Medical Center); *Paula Rhyner, PhD* (Professor of Communication Sciences & Disorders, UWM and Interim Associate Dean for Research, College of Health Sciences, UWM*); Tina Yen, MD* (Associate Professor of Surgery, MCW); *Michael Widlansky, MD* (Associate Professor of Medicine, MCW); *John Densmore, MD* (Assistant Professor of Pediatric Surgery, MCW*); Allison Hyngstrom, PhD* (Assistant Professor of Physical Therapy, Marquette).

In the future, we will add a basic scientist, a hospital representative, and a community member to the review group. The KL2 director will function as a non-voting administrator of the review group. Applications will be scored using the NIH scale, and funding decisions will be made by the Executive Committee of the CTSI. Invariably, funding decisions in the past have been based on the priority scores.

Program Advisory Committee. We propose to establish an advisory committee for the Clinical Research Training Program. The committee will oversee and provide recommendations for all aspects of the program's recruitment, training, and mentoring strategies. The committee will include representatives from the Medical College of Wisconsin (MCW), the University of Wisconsin-Milwaukee (UWM), Marquette University (MU), and the Milwaukee School of Engineering (MSOE), and industry. Additional member will include Dr. David Brousseau, Director of the propose START program (TL1) and Dr. David Harder, Associate Director of START and MCW Associate Dean for Mentoring.The committee will meet at least every six months, and the agenda will be established jointly by the chair of the committee and the director of the training program.

B. PROGRAM FACULTY (MENTORS)

Mentoring plays a vital role in the career development and overall success of researchers across a wide range of disciplines, including academic medicine (13,14). In 2010, a team from five CTSA institutions adapted a mentor training curriculum developed by the University of Wisconsin-Madison CTSA to make it applicable to clinical and translational researchers (15,16). The curriculum addresses the following six mentoring competencies: a) maintaining effective communication; b) aligning expectations; c) assessing understanding; d) addressing diversity; e) fostering independence; and f) promoting professional development. A subsequent randomized controlled trial demonstrated that this competency-based mentor training program improves mentor's skills. Approximately two years ago, the training curriculum was beta tested with 15 faculty at our CTSI, and it was well received. We anticipate offering this training to potential mentors at least every other year. As we develop mentoring teams for future clinical research trainees, we will require completion of the mentor training curriculum for the lead mentor of each mentoring team. The program's Advisory Committee will semi-annually evaluate each trainee's progress as well as the contributions of the mentors. If the mentor-mentee relationship is not proceeding satisfactorily, the Committee may recommend replacing a mentor.

Currently, there is a cadre of at least 36 mentors who have contributed to mentoring clinical/translational investigators. They represent a wide spectrum of departments and disciplines (see Table 5B). All are federally funded investigators. In addition, we are also including recently funded clinical research trainees as members of our "core faculty" (see **Appendix XX for biosketches**).

An additional resource is available at MCW to assist in the identification, recruitment and development of research mentors. The Research Mentoring Program, established by the MCW Office of Research, provides long-term mentoring for research-intensive faculty from hire to first federal funding and through to grant renewal. The overall goal of the program is to increase sustainable grant success by research-intensive faculty. Led by Gilbert White, MD, Associate Dean for Research, a task force formulated an operational plan that, at the request of the Departmental Chair, links faculty members with a mentoring team that includes senior expert research mentors. Composition of individual mentoring teams is recommended by a Mentoring Oversight Board, whose membership includes 12 campus research leaders. Mentors are experienced researchers with intimate knowledge of the NIH and other national funding agencies. Prior service on study sections is especially advantageous. Currently, 165 mentors at MCW have been vetted by this program. The Office of Research maintains a faculty database that is used to identify potential mentors. The database, which is accessible by all CTSI partner institutions, contains research interest, experimental technologies, grant funding, and service on study sections. This resource will be available to assist clinical research trainees identify research mentors.

The mentoring team will periodically review progress along the trainee's Career Development Plan and assist trainees to develop grant applications and successfully compete for research funding. Each trainee's mentoring team will include the following:

a. Lead mentor. Individuals selected for this position will have completed the training curriculum for clinical and translational researchers, described above.

b. Career navigator. This individual will ensure that trainees are taking the necessary steps to advance their careers as clinical investigators. This is critical because we have learned that trainees often feel overwhelmed by the apparently competing priorities of research and patient care.

c. Research mentors. These individuals will have relevant research expertise in both basic and clinical sciences. They are encouraged to focus the mentee on research that will lead to funding. They will be expected to provide critical review of drafts of manuscripts and grant applications.

d. Community member or patient. This individual may provide a different perspective regarding the potential impact of the trainee's research agenda.

The program's Advisory Committee, in conjunction with the trainee's Department Chairman, will recommend the composition of each trainee's mentoring team. The trainee will meet with his/her mentoring committee on a scheduled basis, 3 or 4 times per year, and more frequently as necessary. Minutes from these meetings will be logged, and progress as well as action plans will be documented. This information will be shared with the trainee's Department Chair. Members of the mentoring committee will also be expected to be available to meet with the trainee more frequently on an individual basis.

C. PROPOSED CAREER DEVELOPMENT PROGRAM

Overview

*The overall goal of the Mentored Clinical Translational Research Training Program is to facilitate the research career development of early-stage clinical/translational investigators***.**

The CTSI Mentored Clinical Translational Research Training Program is intended to equip the next generation of clinical and translational scientists with the tools to facilitate and accelerate the translation of basic science discoveries into clinical care and improvements in health. The program provides early-stage investigators with research training, funds and time to engage in inter-professional educational opportunities (workshops/conferences, etc.), and opportunities to collaborate with and learn from other early stage and experienced investigators from different disciplines. The program will integrate team science into trainees' research development by imbedding trainees as active members of multidisciplinary research teams that include clinical and basic science investigators. Evaluation of the program will focus on its impact on research productivity and career trajectories of trainees.

Resources and Partnerships

Medical College of Wisconsin. MCW 's mission is to discover and translate new knowledge in the biomedical sciences, provide cutting-edge interdisciplinary and compassionate clinical care of the highest quality, and improve the health of the communities we serve. With ~1,600 full time faculty and ~3,450 full time staff, MCW is the largest private academic medical center in Wisconsin. It operates 26 academic departments and many diverse federal and institutional research centers. Our physicians provide a wide spectrum of adult patient casr as Medical College Physicians and pediatric care through Children's Specialty Group, a joint venture with Children's Hospital and Health System. MCW providers practice at three major hospital affiliates—Froedtert Hospital, Children's Hospital of Wisconsin, and the Zablocki VA Medical Center, as well as at other clinics and collaborative hospitals in the Milwaukee area. In 2012-2013, MCW physicians provided care to more than 425,000 patients, representing more than 1.6 million patient visits. Access to patients for clinical research is

facilitated by the use of electronical medical records in the hospitals and clinics, and by the CTSI's development of a *clinical data warehouse*. The warehouse integrates medical records, patient registrations, and laboratory and tissue bank data and translates data from a patient care system to a research-based system. Currently, data from the entire Froedtert Health System (hospitals and clinics) include one million individuals. With a grant from PCORI, this warehouse will shortly interconnect with 10 other academic centers, 8 of which have CTSAs. It will include data for 12 million people. Additionally, plans are to include Childrenl's Hospital network, which will include 500,000 people.

MCW faculty supervise ~ 650 physicians in residency training and 200 physicians in fellowship training throughout its affiliated hospitals and clinics. There are more than 1,200 students enrolled in educational programs at MCW, including 820 medical students and more than 400 graduate students..
Growth of collaborative basic science and clinical/translational research at MCW has evolved around our centers-based research themes. These centers encourage and facilitate multidisciplinary research across departmental boundaries. These include the following:

Federally Designated Centers

- National Biomedical Electron Paramagnetic Resonance Center
- National Center for AIDS Intervention and Research
- National Center for Systems Biology
- National Southeast Wisconsin Clinical and Translational Science Institute
- National Injury Research Center
- National Research Center of Excellence in Pediatric Nephrology
- Wisconsin Center of Excellence in Genomics Science

International Center, Centers and Institutes

- Biotechnology and Bioengineering Center
- Cardiovascular Center
- Center for Bioethics and Medical Humanities
- Center for Imaging Research
- Center for Infectious Disease Research
- Center for Patient Care and Outcome Research
- Digestive Disease Center
- Human and Molecular Genetics Center
- Center for International Blood and Marrow Transplant Research
- Institute for Health and Society
- Neuroscience Research Center

In fiscal year 2013, MCW ranked 43rd among the nation's 138 medical schools for NIH research funding, and among the top50 schools of medicine, MCW ranked 3rd for dollars per award. In FY14, faculty received more than $154 million in external support for research, teaching, and related purposes, of which more than $138 million was allocated for research ($79.5 million from NIH). MCW is the largest research institution in the Milwaukee metro area and the second largest in Wisconsin. MCW is particularly distinguished for excellence in cardiovascular disease, genetics, cancer, imaging, bone marrow and kidney transplant, and pediatrics. In 2013, MCW has advanced in all areas of research, including translational sciences, clinical trials, and in the T3-T4 research arenas. Additionally, the College has 220 pending and issued patents, and has research and development affiliations with other major universities and research institutions, as well as government and venture capitals groups. The College has launched 18 start-up companies and licensed technologies to more than 50 pharmaceutical, diagnostic, biotechnology, and medical device corporations.

Affiliated Academic Institutions. In 2006, with the support of a CTSA pilot grant, MCW expanded its formal relationships with several other academic institutions in the region—*University of Wisconsin/Milwaukee (UWM), Marquette University (MU), and the Milwaukee School of Engineering (MSOE).* UWM faculty received 275 external awards totaling $27.8 million, including 45 NIH awards totaling $6.8 million. MU received funding for 182 awards, totaling $24.4M, including 42 awards totaling $5.7M from NIH. MSOE received $3.6 million for teaching and research programs. We now have in place a CTSI with these institutions, MCW, MCW's hospital affiliates, the Children's Research Institute, and the Blood Center of Wisconsin as partners. This partnership includes schools of nursing, dentistry, physical therapy, health science, and public health. Faculty and leadership from each of these schools are currently participating in the activities of the CTSI. In fiscal year 2014, UWM faculty received 275 external awards totaling $27.8 million, including 45 NIH awards totaling $6.8 million. MU received funding for 182 awards, totaling $24.4 million, including 42 awards totaling $5.7 million from NIH. MSOE received $3.6 million for teaching and research programs.

Affiliated Research Institutes. The Children's Research Institute (CRI) is part of the Children's Hospital of Wisconsin and is affiliated with MCW. Investigators at the CRI advance state-of-the-art pediatric health care through basic and translational research programs. Over the past eight years, NIH funding to the Department of Pediatrics, a partner with the CRI, has risen from 37th to 21st. The Blood Research Institute (BRI) is a state-of-the-art facility; that houses cutting-edge research equipment and related specialized services. BRI faculty include 16PhDs, 11 MDs, and 4 MD/PhDs involved in research related to blood disorders thrombosis, hemostasis, and mechanistic research in vascular biology. In fiscal year 2014, NIH funding to the BRI was $13.1 million for 30 awards. Dr. Gilbert White, Director of the BRI, is a member of the CTSI Executive Committee.

Summary. The CTSI partners include MCW, Froedtert Hospital, Children's Hospital of Wisconsin, the Zablocki VA Medical Center, UWM, MU, MSOE, and the BRI. This partnership provides an enriched environment for multidisciplinary research collaborations, as well as for recruiting and training clinical investigators.

Previous experience

The proposed clinical investigator training program is based upon our assessment of the current opportunities and barriers for a research-oriented career and upon our experience with clinical investigator training. We briefly summarize this experience.

Clinical Research Scholars' Program. Prior to its funding through the Clinical and Translational Science Institute (CTSI), this program was funded for 10 years through the NIH K30 mechanism. The overall goal of the CRS Program is to prepare scholars to function effectively as productive clinical investigators. The CRS educational endeavors are tailored to meet the needs of individual scholars through participation in clinical research, mentoring, identification of appropriate resources (including funding opportunities), and enhancement of the scholars' multidisciplinary research colleague-network, both within the partnering CTSI institutions and through external collaborations. In addition to a primary mentor and mentoring committee, a biostatistical advisor is assigned to each scholar. Scholars develop individual career development plans, with specific goals, activities and benchmarks for achievements. The program meets bi-weekly for two-hour sessions consisting of both large-group didactic sessions and small-group sessions in which the research efforts of the scholars are discussed. The two-year curriculum provides explicit instruction in ethical conduct of research, application of innovative concepts and new technologies to research, scientific communication through publications and presentations, preparation of competitive grant applications and research project management.

Since its inception in 1999, 119 scholars have either completed or are currently in the program. Sixty-four of the scholars are female, 9 are UWM faculty, and 5 are Marquette faculty. The remainder are MCW faculty. A number of academic departments are represented (e.g., Medicine, Pediatrics, Surgery, Psychiatry, Neurology, Family & Community Medicine, Dentistry, Otolaryngology, Physical Medicine & Rehabilitation, Dermatology, Engineering & Applied Science, Health Sciences), and of the larger departments, several divisions are represented. Twenty-two scholars are Asian, 6 are African American, 1 is Hispanic, 1 is ethnicity unknown,

and 89 are non-Hispanic white. Approximately one-third of the scholars also participate in the Master of Science in Clinical and Translational Science Program at MCW. Most of the scholars have received funding for their research. Based upon research productivity (grants received, publications and presentations) as well as satisfaction on the part of participants, the Program has been deemed successful.

Mentored clinical research training program. This program was introduced in 2005. Since that time, 17 early-stage investigators (assistant professors) have participated in the program. Between 2005 and 2010, prior to the NIH CTSA award, all trainee positions were supported by Medical College of Wisconsin funds, and all trainees were Medical College faculty. Subsequently, trainee positions were supported by NIH or institutional funds, and NIH-supported positions were supplemented with institutional funds. Since 2011, NIH funds have been contributing to the support of 6 trainees---3 at MCW, 1 at UWM, and 2 at MU. Programmatically, there has been no distinction between NIH funded and Institution funded trainees. Eligibility criteria for all trainees have primarily been based on criteria for the NIH K23 award.

From the perspective of the numbers of publications and extramural research funding, trainees have been successful. The 12 trainees who have completed the program have reported 86 publications in peer-reviewed journals, and while in the program, trainees have published an average of 5 peer-reviewed manuscripts per trainee in more than 50 journals, reflecting the diversity of disciplines represented by the trainees. All former and current trainees have successfully competed for local and/or foundation research support. As shown in the table below, all but 3 former trainees and 2 current trainees have federal funding for their research.

Table 1. Synopsis of former and current trainees

Initial year of Award	Name	Inst	Trainees' Dept	Research focus	Outcomes To be added
FORMER TRAINEES					
2005	Raymond Migrino, MD	MCW	Med/Cardiol	Cardiac amyloidosis	VA Merit—PI NIH R21—PI 2 NIH RO1s-- colllab AHA, Am Can Soc
2005	Michael Stevens,MD	MCW	Ped/GI	Inflammatory bowel disease	NIH K08 Colitis Fdn--PI
2005	Amy Hefflefinger, MD	MCW	Ped/Neurol	Neuropsychologic functioning in pre-schoolers and adolescents	Sarah Jane Brain Fdn--PI
2008	Michael Widlansky, MD	MCW	Med/Cardiol	Vascular endothelial dysfunction in diabetes	NIH K23—PI NIH R01 co-PI Doris Duke—co I AHA—PI
2008	Vidya Kidambi, MD	MCW	Med/Endo	Metabolic syndrome	AHA---PI
2008	Kevin Regner, MD	MCW	Med/Nephrol	Mechanisms of acute renal injury	NIH R01—coPI NIH R25--PI
2008	Hao Zhang,PhD	UWM	Electrical Engineering	Functional imaging in diabetic eyes	NSF—PI NSF—co I NIH challenge grant---PI
2011	Jonathan Bock*, MD	MCW	Otolaryngol	MicroRNA profiling in squamous cell carcinoma of head and neck	
2011	Masha Ranji*, PhD	UWM	Electrical Engineering	Mechanism of lung injury	NIH 2 R01s—co I VA Merit—co I

2011	John Densmore,MD	MCW	Surg/Ped	Acute lung injury	VA Merit—co I NIH R01—co I
2011	Allison Hyngstrom*, PT/ PhD	MU	Physical Therapy	Neuromuscular rehabilitation	NIH R21—PI NIH R15—PI NIH R21—co I NIH R01—co I
2012	Venkatesh Sampath, MD	MCW	Ped	Gene-environment interactions in bronchopulmonary dysplasia	NIH R03—PI NIEHS—PI NIEHS—PI
CURRENT TRAINEES					
2013	Arash Babaei, MD	MCW	Med/GI	Neuromuscular control of deglutition	NIH R56—co I
2014	Erin Bishop*, MD	MCW	Ob/Gyn	Molecular mechanisms of pathogenicity and therapeutic resistance in breast cancer	
2014	Amy Van Heckle*, PhD	MU	Psychology	Autism	
2014	Carmen/Bergom MD/PhD	MCW	Radiation Oncology	Molecular mechanisms of therapeutic resistance in breast cancer	
2014	Guilherme Garcia*, PhD	MCW	Otolaryngol	Pharyngeal compliance in obstructive sleep apnea	NIH 2 R01s—co I

- *Funded by NIH, others supported by institutional funds

We have recently surveyed all former and current clinical research scholars (formerly called K30) and KL2 scholars, inviting them do carry out a SWOT(Strengths, Weaknesses, Opportunities, Threats) analysis of the program, and several of their recommendations have been incorporated into the present proposal.

Engagement in multidisciplinary, collaborative research was the most striking predictor of obtaining extramural funding. These outcomes document our ability to successfully mentor clinical researchers across several disciplines and highlight our rationale for focusing on team research. We view the research diversity of our trainees as a distinct advantage, as it promotes multidisciplinary problem-solving within our program and facilitates multidisciplinary collaborations. The proposed training program will further exploit this advantage.

As part of our evaluation of the existing Clinical Research Scholars program (formerly called K30) and Clinical Research Training program, we have recently surveyed all former and current clinical research scholars and clinical research trainees, inviting them do complete a SWOT(Strengths, Weaknesses, Opportunities, Threats) analysis of the program. A number of innovative suggestions from this exercise have been incorporated into the present proposal, including the identification of a comprehensive mentoring team for each trainee, strategies to assure each trainee is incorporated as an active contributor to a research team, and development of a supportive peer group of trainees.

Program objectives and curriculum

The proposed comprehensive curriculum includes didactic coursework, mentored clinical research training, emphasis on mentored multidisciplinary research collaborations, and opportunities for apprenticeships in the community and with industry. The training program is sufficiently flexible to accommodate trainees with different backgrounds, different levels of experience, and different research career trajectories. The program's Advisory Committee, the KL2 Director, the trainee's career navigator and mentoring team will provide advice regarding the individualized training curriculum.

Objective 1. Assist each trainee in creating an individualized, comprehensive, and goal-focused *research career development plan*.

The program is sufficiently flexible to accommodate trainees' expectations to attain independent research funding as well as to accommodate trainees learning to leverage clinical skills to participate as a leading or contributing member of a multidisciplinary research team. The program will accommodate the needs of trainees with an anticipated career trajectory in basic research, patient-oriented research, or population-based research. As recommended by the Evaluation Committee of the Association for Clinical Research Training (17), our intent is to prospectively individualize the curriculum by delineating the knowledge and skills (competencies) to be acquired by each trainee.

To assist in formulating a research career development plan and career goals, trainees will be encouraged to use a FASEB online assessment tool. This tool provides guidance for the selection of the mentoring team and for the recommended coursework to augment the plan. Dr. Phil Clifford, a former graduate of MCW's doctoral program in Physiology and former Associate Dean of the MCW Graduate School and Office of Postdoctoral Education, was the lead author of the publication describing this career planning tool (18). By working through this guide, strategic goals can be prepared and serve as part of the milestones set up with the trainee, the training program Director, and the mentoring team.

Related activities:

1. Link each trainee with an experienced and trusted *career navigator*.
2. For each trainee, develop core competency requirements, specific career goals and timelines for attainment.
3. Provide opportunities for relevant didactic learning, including a master's degree in Translational Science
4. Orient Scholars to a variety of research career options and funding sources.
5. Provide opportunities for apprenticeships in a community-based program or with industry.
6. Provide increased opportunities for leadership training, e.g., UWM/MCW Leadership training course, mentoring junior colleagues.
7. Maintain supportive relationships with trainees who have completed the program.
8. Create a peer support group for former and current trainees to focus on the following:
    a. Career opportunities and barriers to career development
    b. Multidisciplinary research team collaboration

Objective 2. Integrate team science into research career development.

We have re-learned what we already knew—the likelihood of a successful research-oriented career and having a scientific impact is enhanced by being a member of a multidisciplinary research team. Investigators working in isolation have a greater likelihood of becoming lost to the clinical/translational workforce. Multifactorial health problems and the rapid advances of technology require investigators to adopt multidisciplinary, collaborative research approaches (19). Fostering greater collaborations among scientists trained in different fields is an essential strategy for ameliorating these complex problems (20); and creativity and innovative thinking are encouraged when innovations in one domain address problems in a new domain (21). Investigators that work collaboratively on multidisciplinary teams are more productive, produce higher impact research, and are positioned to address more complex problems than scientists working solo (22, 23). These

considerations compel research training programs to adopt cross-disciplinary theoretical and methodological tactics that focus on team science. Team science is defined as a "collaborative effort to address a scientific challenge that leverages the strengths and expertise of professional trained in difference fields" (24). The ultimate goal of team science is to accelerate scientifically-based strategies for the prevention, evaluation, and treatment of disease.

Additionally, an effective team needs good leadership, a shared vision, clear expectations, regular meetings shared knowledge, constructive criticism, trust, and conflict management (25). Members continuously and simultaneously compete and cooperate with one another in a complex and fast—moving social network that benefits both the team and the individual members (26).

Related Activities

1. Establish the requirement that eligibility for the program will require the identification of a relevant multidisciplinary team
2. Applicant review committee to evaluate the likelihood of the applicant's potential to meaningfully participate in the team.
3. For each trainee, create a *Multidisciplinary Project Development Panel* to assist in the identification of team members.
4. Incorporate into the team a community member or patient who is affected by the medical problem/issue being studied.
5. Career navigator to assure that each trainee is imbedded within a team.
6. KL2 program director to assure that each trainee defines his/her unique contribution to the team.
7. If necessary, provide limited financial support to develop a team-based research proposal
8. Develop metrics to evaluate team participation.

Didactic learning. KL2 trainees who have not previously completed the *Clinical Research Scholars program* (formerly K30) will be required to concurrently participate in that program. The major points of emphasis in that program include communication skills, grant and manuscript writing, time and research management, and career development. All KL2 trainees will be required to take a 1-credit seminar course, *Introduction to Clinical and Translational Science.* The course is designed to give trainees an introduction to concepts and culture underlying translational research, which entails moving basic or clinical science discoveries to clinical practice and enhancing the health of the public. Conceptual themes conveyed though the course include: creative thinking across traditional boundaries; engaging in discovery through overcoming barriers and problem solving. The course uses case studies which illustrate the conceptual framework and the process of translational research. Additionally, all trainees will be required to take a course in *Leadership Development*, jointly sponsored by UWM and MCW, and a course in Good Clinical Practice that is currently being developed.

Trainees will have the option of obtaining a MS degree program in Clinical and Translational Science, a degree program that was established at MCW in **2010.** This includes courses in epidemiology, biostatistics, integrity in science, clinical trials, introduction to intellectual property, and grant writing. One-third of former or current Clinical Scholars, and 4 of 17 trainees have opted to complete the MS program; however, each of these courses also is available to trainees, whether or not they intend to complete the MS program.

Additionally, in 2011 Marquette and MCW jointly established an MS and PhD program in Clinical and Translational Rehabilitation Health Sciences (Program Director, Paula Papanek). The program currently has 24 MS and PhD students with backgrounds in exercise science, physical therapy, and nursing. This program, or courses within the program will be available to trainees.

With support from a AAMC grant, this fall the CTSI held a workshop, entitled "Building collaborations for patient safety and quality improvement." One outcome of the workshop is the development of a course, entitled "Patient safety and safety science" that will be offered for the first time in spring 2015. Trainees also will be encouraged to explore options for relevant short courses at other hubs or elsewhere, e.g., NIH currently offers a 2-week course on how to conduct clinical trials.

Mentored research. We will assist trainees and potential trainees in becoming imbedded in a multidisciplinary research team. Various strategies for developing multidisciplinary translational research teams have recently been described by CTSA investigators at two different institutions (27,28). Similarly, our CTSI is developing an infrastructure to assist investigators in establishing a multidisciplinary team and to assist the team in developing a specific research proposal. As detailed elsewhere in this application, our CTSI's Office of Regional Expanding Collaborations (OREC) sponsors 3-4 workshops/year focused on specific topics aligned with the interests of the stakeholders, with the primary intent of facilitating the development of multidisciplinary research teams. Team science groups that evolve from the workshops will have the opportunity to apply for a Proposal Development Grant.to develop a research proposal directed at a specific intramural or extramural RFA that includes a team science approach. The CTSI will provide the infrastructure to assist with the development of these proposals. Although this is only one strategy for identifying teams, these resources will be available to prospective and awarded clinical research trainees.

To accommodate individual needs of trainees, we will be able to arrange apprenticeships in the community and with industry.

Potential opportunities for community-based research. MCW has a significant commitment to community engagement, and consequently has access to communities throughout the state that might serve as "laboratories" for trainees pursuing community-based research. Since 2004, the Advancing Healthier Wisconsin endowment to MCW, through the Healthier Wisconsin Partnership Program, has awarded $164.8 million to 311 initiatives through academic/community health partnerships for research, and education. The endowment invests in targeted health priorities: identified measurable outcomes, health priorities, affected populations, and focus areas in order to maximize impact, utilize evidence-based resources and practices, and promote sustainability. The 2014-2018 five-year plan targets investments in the following areas: strategic initiatives that include large, long-term initiatives to improve health; responsive initiatives that invest in community-identified needs to overcome barriers to health improvement; capacity-building initiatives that strengthen community capacity and leadership to support health improvement; and cross-cutting initiatives that bring together the unique strengths of diversity, community-partnerships, research, and education to address Wisconsin's leading causes of death and disability.

The UWM Joseph J. Zilber School of Public Health was founded in 2012, and Magda Peck, ScD, the founding dean, has become an active participant in the CTSI. We are developing collaborative research initiatives, and Dr. Peck recently chaired a CTSI-sponsored workshop dealing with women's health. Collaboration with the School of Public Health makes new community-based research opportunities potentially available to trainees. Several School of Public Health faculty are conducting community based research, including using community-based participatory research approaches. Drs. Alice Yan, Paul Florsheim, Renee Walker, Emmanuel Ngui and Lance Weinhardt, all members of the Community and Behavioral Health Promotion faculty within the School of Public Health have current projects which could involve CTSI trainees. The research spans areas from diet and exercise promotion among cancer survivors, to interventions to improve involvement of young unwed fathers in the lives of their children, to HIV prevention. These projects are funded by a variety of local, state, and federal agencies. Further, Dean Peck has held an RC4 grant from NIH specifically to translate research findings into community action around maternal and child health, and is considered an expert in translational community engaged-research.

The CTSI'sCommunity Engagement Core will facilitate access to community-based research.

Opportunities in industry. Each of the academic partners within the CTSI has a unique relationship with General Electric (GE) in the area of research and product development that can be leveraged to broaden the experiential learning offerings of the Program. UWM has received substantial financial support from GE Global Health to support proof of principle studies related to product development. MU collaborates with GE on product development in the magnetic resonance imaging (MRI) arena. We can exploit MCW's unique relationship with GE Global Health to serve as an active partner conduit between commercial development and clinical application. A case in point is MCW's partnership with GE Health and the State of Wisconsin that has resulted in the purchase and installation of the first state-of-the-art 7 Tesla whole body self-shielded MRI imaging device. This equipment is so new that substantial development is needed before it can obtain

regulatory clearance. A team of engineers from GE and MCW as well as MSOE are working together to develop this technology that is anticipated to revolutionize the imaging world by offering for the first time, resolution at the cell layer level. This team of investigators, led by Dr. Shi- Jiang Li serves as an excellent source of mentors for appropriate KL2 applicants. Additionally, MCW and UWM are working to define novel uses of ultrasound imaging in conjunction with GE.

Postdoc Industry Consultants (PICO) is a bioscience consulting group comprised of post-doctoral fellows at MCW and UWM. The goal is to provide research-based, short-term consulting services to biotechnology and pharmaceutical firms, while providing fellows with first-hand experience in industry and work on projects that positively impact local bioscience firms. Consulting teams are made up of two or more post-doctoral fellows. Projects are generally completed within 2-6 months, and each team member commits approximately 5-10 hours/week. Interested clinical research trainees will have the opportunity to join one of these consulting teams. Since its inception in 2011, PICO has completed more than 30 projects with 16 companies. Based on modeling the PICO program, and with PICO's assistance, the CTSI will develop similar industry-based consulting opportunities for clinical research scholars and KL2 trainees.

Table 2 summarizes the Elements of the Curriculum:

Required	Optional
Individualized Career Development Plan	MS in Clin/Trans Science
Clinical Scholars Program	Additional Courses
Mentored research plan	Visits to other hubs
Courses:	Short-term "apprenticeships"
Introduction to Clin/Trans Science	Industry
Good Clinical Practices	Community
Leadership Development	Others
Ethics and Integrity in Research	
CITI certification	

Our CTSI has developed a robust clinical research training program that is unique in southeastern Wisconsin. The resources for didactic learning, research, and mentoring are already in place. Future innovations are related to increased emphasis on team science and career development. The training program has been well received and is enthusiastically supported by the leadership of each of the CTSI's partner institutions. Department chairs have assured trainees of the required protected time for their training and research, and have financially contributed to their support.

D. INTEGRATING PROPOSED PLAN WITH A BROADER VISION OF THE WORKFORCE NEEDED TO DRIVE FUTURE INNOVATION AND IMPLEMENT EFFECTIVE C-T RESEARCH

An underlying premise of our training program is that participation as a member of a multidisciplinary team optimizes the likelihood of the research having an impact and of the trainee having a successful research career trajectory. From our own program, we can cite several examples of productive collaborations involving apparently disparate areas of expertise:

a. Allison Hyngstrom, PT, PhD, a former KL2 trainee, is an assistant professor of Physical Therapy at Marquette University. The long-term objective of her research is to develop treatment interventions that will optimize strength training and improve walking in post-stroke patients. During the time she was a trainee in our Clinical Research Scholars program (formerly K30) and the KL2 program, she developed meaningful collaborations with a physiologist and a clinical investigator at MCW. She received two CTSI Pilot awards to support this collaborative research. As an extension of these projects, she is currently Principal Investigator of a funded R21 (Impaired blood flow and neuromuscular fatigue post stroke) and a funded R15 (Neural mechanisms of neuromuscular fatigue post stroke) grant. She is also co-Investigator of an additional R21 grant and a R01 grant.

b. Hao Zhang, PhD, a former trainee in the KL2 program who at that time was an assistant professor of in the Department of Electrical Engineering at UWM. He developed collaborative relationships with MCW faculty in the Department of Ophthalmology to develop methodology to study retinal functional imaging in patients with diabetic retinopathy. He subsequently accepted a faculty position at Northwestern University at the level of associate professor. Currently, he is principal investigator of an R01 grant with a clinical collaborator as co-investigator (Multimodal retinal

functional imaging for diabetic retinopathy). In addition, Dr. Zhang is principal investigator or co-investigator of several other NIH and NSF grants related to retinal imaging and diabetic retinopathy.

c. Mahsa Ranji, a former KL2 trainee has a PhD degree in Electrical Engineering. She has recently been promoted to associate professor in the Department of Electrical Engineering at UWM. In conjunction with her mentor, Elizabeth Jacobs, MD, professor of Medicine at MCW, Dr. Ranji is co-investigator of a VA Merit Review grant (Mitochondrial redox studies of cardiopulmonary oxidative stress) and an R01 grant (Novel imaging to identify lung mitochondrial injury an predict recovery). She is also co-investigator of another R01 grant and has a pending R01 submission to NIH as principal investigator.

d. Guilherme Garcia, a current KL2 trainee, has a PhD degree in physics. His primary mentor, John Rhee, MD, MPH, is Professor and Chairman of the Department of Otolaryngology and Communication Sciences at MCW. Dr. Rhee is PI and Dr. Garcia is co-investigator of a recently funded R01 grant, entitled "Creating virtual surgery targets and methods to improve outcomes of nasal airway surgery". Dr. Garcia is also co-I of a pending R01 grant (scored in the 5th percentile) of another of his mentors, Julia Kimbell, PhD, Associate Professor of Otolaryngology at the University of North Carolina. That grant is titled, "Improving topical drug delivery for treatment of chronic rhinosinusitis."

e. Kevin Regner, MD, is an Associate Professor in the MCW Division of Nephrology and was appointed as Interim Chief of Nephrology in 2013. The objective of his research is to study mechanisms of acute renal failure. Before receiving the KL2 award, he was a trainee in the Clinical Research Scholars program. During the time he was a KL2 trainee, he completed a Master of Science Degree in Clinical and Translational Science. After completing the program, he successfully competed as Principal Investigator for an R01 grant, funded by NIDDK to study mechanisms of ischemic renal injury. His collaborator for the project is Frank Park, PhD, in the Department of Pharmaceutical Sciences in the College of Pharmacy at the University of Tennessee Health Sciences Center. Dr. Regner is a significant role model for our mentoring programs in that he has become a leader in training. In 2013, he was awarded an NIDDK-funded R25 research education grant to support 5 medical students annually for summer research training with the aim of encouraging them to persue careers in translational research related to kidney diseases.

As another example of a productive multidisciplinary collaboration emanating from our KL2 program, Dr. Allison Hyngstrom, a former KL2 trainee (see above), helped establish a collaboration between MCW Department of Physical Medicine and Rehabilitation (PMR) and Marquette University. This collaboration is part of the recently formed Neural Rehabilitation Research Center (NRC), with an emphasis on stroke. The NRC is under the direction of Drs. Diane Braza (Chair of PMR at MCW) John McGuire (Associate Professor of PMR and MCW), along with Drs. Brian Schmidt (Professor of Biomedical Engineering at Marquette) and Jean Hosenpud (Marquette). PMR fellows rotate through research laboratories that are actively engaged in stroke rehabilitation research at Marquette. Currently two fellows spend 1 day/week in their assigned laboratories at Marquette (Dr. Brian Schmit, Biomedical Engineering and Dr. Allison Hyngstrom, Physical Therapy). Fellows are engaged in specific research projects and are obtaining skills in data collection, analysis, manuscript preparation, and the IRB process. The research rotation begins with a 2-3 week immersion in the research laboratories at the start of their clinical fellowships. Additionally, selected students from physical and occupational therapy departments in academic institutions in Southeast Wisconsin will rotate through academic laboratories and through a proposed clinical laboratory to engage in translational research. Graduate students will observe clinics for stroke survivors and engage in the clinical laboratory to understand specific opportunities for improving movement in stroke survivors.

Collaboration with other hubs is a priority for the CTSI. MCW is a member of the Midwest Area Consortium for Health (MARCH). Other members of the consortium include Indiana University, Mayo Clinic, Ohio State University, University of Minnesota, and University of Wisconsin-Madison. The consortium was established to facilitate collaborative clinical research across CTSA hubs. There is a single coordinating center (currently at University of Wisconsin-Madison, with plans to rotate), a single administrative director, a single contract, and

all members of the consortium have approved a single IRB. Although this is a new venture, MCW investigators have brought 2 clinical trials into the consortium.

To further facilitate collaborative research across MARCH hubs and those of other CTSAs, we propose to hold a regional or national workshop that would give trainees at different hubs an opportunity to interact with each other, and might lead to new collaborations across hubs. Our CTSI currently sponsors 3-4 workshops per year, with the primary intent of developing new research collaborations among the CTSI's partner institutions. We have developed metrics to evaluate this outcome, and propose that similar metrics be applied to a trainees' workshop across hubs. We would be pleased to participate in the planning, or host such a workshop.

E. PROGRAM EVALUATION

Several metrics will be used to evaluate trainees and the training program**.** The Evaluation Committee of the Association for Clinical Research Training has proposed a logic model and accompanying data collection plan to aid in the evaluation of translational research training programs (17) (see Appendix 1). Short-term outcomes (training changes) include trainee satisfaction, increase in clinical research self-efficacy, and an increase in the number and quality of professional relationships. Intermediate intended outcomes include the conduct of effective multidisciplinary studies, submission and publication of research manuscripts, submission and received funding proposals, as well as scholars mentoring other early-stage investigators and scholars maintaining time for their own research.

Consistent with these recommendations, each of these short-term and intermediate-term outcomes will be monitored in our program. Universally accepted metrics for career success across CTSAs typically fall into two domains – intrinsic and extrinsic career success factors (29). Our program evaluation will focus primarily on extrinsic career success factors such as promotions, leadership positions, grants and publications. In 2012, CTSI implemented an online tracking tool developed by the Rockefeller Univ. CTSA, called the Graduate Tracking Survey System (GTSS). The GTSS captures individual-level data (e.g., publications, presentations, funding, clinical trial participation, patents and technology transfer products and appointments), on education participants utilizing four public databases and request that the respondents validate their products. All CTSI education participants, including trainees, update a GTSS profile annually, provide respective program feedback, report time spent on research, teaching and mentoring, and report any collaborators they might be working with to advance their research and training. Trainees also report on any scientific or medical paradigm changing discoveries that have come from their research via the GTSS. While these serve as annual productivity measures for Scholars, short-term success is defined as submission of a grant proposal for funding. Scholars are expected to re-submit positively reviewed applications that may not have been funded, and mentors are pivotal to this process.

To assess more immediate program outcomes, the CTSI will utilize the Clinical Research Appraisal Inventory (CRAI) (see Appendix 2) (30-33).Acquisition of independent funding is a widely accepted indicator for success and stability of a clinical investigator; however, for many early-stage investigators, this may not occur until several years after completing a training program. As a result, evaluation data aim to capture more immediate indicators of program success, including program satisfaction, training-program relevance to one's career path, and research self-efficacy. The CRAI assesses trainees' clinical research self-efficacy or confidence in one's ability to perform clinical research-related tasks (e.g., designing research study, collecting data, interpreting, reporting, presenting, etc.), as a short-term indicator of program impact. Trainees will complete the CRAI at entry into the program and again at the end of his/her KL2 award. The CRAI is utilized at a number of other CTSAs to evaluate intermediate program outcomes. We will utilize a shortened version of the CRAI, as the 12-item CRAI is faster and less burdensome to complete, while retaining strong psychometric properties of the original CRAI (32) The CRAI also will be administered to those participating in our TL1, Clinical Research Scholars program, and our Master's in Clinical and Translational Science degree program. Since the environments in which faculty work can influence their scholarly and research productivity, trainees also will complete upon entry and exit of the program an 'Environmental Characteristics' instrument that gathers the trainee's perceptions on aspects that influence research productivity for their department and primary worksite (see appendix). CTSI has utilized the results of this survey to monitor how department and primary work settings influence a trainee's ability to produce scholarly products and research since 2009. In the next five years, we will experiment with providing different work spaces for scholars who rate their environments lower.

Other competencies related to developing transdisciplinary scientists will also be measured (table adopted from ref 34). Strong communication and interpersonal skills are crucial ingredients in establishing effective relationships with other scientists who approach a research problem/issue from other disciplines (34). Trainee competencies in these areas will be assessed two times a year by the program Director, who will utilize a semi-structured interview guide (see Appendix 3) when meeting with trainees for one-on-one meetings throughout their tenure in the program. The Director's assessment of skill development will be included in a written summary of the interview, provided to the CTSI Director and will be reported in our Annual Progress Report and to the trainee's Department Chair.

Table 3. Competency Skill

1. Communication and interpersonal skills
2. Critical-thinking skills
3. Perseverance in overcoming obstacles
4. Patience in knowing that the benefits of taking take time to be realized
5. Inclusive thinking
6. Broad-gauged, contextually oriented theorizing
7. Methodologically pluralist approach

Evaluation data will be summarized semi-annually and shared with program staff and CTSI leadership. Findings are disseminated in partnership with CTSI and its cores, the CTSA consortium and the NIH through various channels. Official evaluation reports, as available are provided to CTSI administration for scheduled reporting periods. Various short reports and presentations are drafted and provided as required for CTSI administration and its oversight committees, as opportunities arise. Preliminary evaluation findings will be presented to the CTSI leadership team and the External Advisory Board on an annual basis (or as necessary). In the next five years efforts will focus on publishing more evaluation reports and data via the CTSI website in an effort to make the attainment of key outcomes more transparent.

F. CANDIDATES/SCHOLARS

In this application, we are requesting support for 2 trainees/year. We anticipate that this support will be leveraged to obtain support from our academic partners for an additional 3-4 trainees/year. Consequently, we will continue to have a core of 5-6 trainees/year in the program.

As in the past, we will rely heavily upon K23 criteria for inclusion and evaluation of applicants to the program. Previously our acceptance rates of applicants into the program have ranged between 10-20%. Potential trainees include full-time faculty (instructor or assistant professor) at any of the CTSI's academic partner institutions (MCW, UWM, Marquette, MSOE). Candidates must either be a US citizen or hold a permanent residency visa. They must hold either a health professional degree or doctoral degree. In contrast to K23 eligibility requirements, the doctoral degree does not necessarily have to be in a health profession. Notably, two of our most successful trainees were PhD faculty in the Department of Electrical Engineering at UWM. Both developed productive collaborations with clinical investigators and with these collaborators, and both have successfully competed for federal funding for their research. However, eligibility criteria for PhD applicants will require that a health professional be a member of the multidisciplinary research team. In the future, we also will add another caveat to the K23 inclusion criteria---an a priori estimate of the likelihood that the trainee will become imbedded in a multidisciplinary team.

Criteria for evaluation of applicants include the following: a) candidate (potential to develop as a clinical investigator, commitment to the program and its objectives, prior research experience, likelihood of becoming imbedded in a multidisciplinary research team, letters of reference); b) well- organized career development plan (based on prior experience, relationship of didactic learning to proposed research, relationship of training and research to other professional responsibilities); c) research plan (multidisciplinary, scientifically sound, relevant to career objectives, appropriate data and safety monitoring plan); d) mentoring plan (mentors'

qualifications, experience, availability, plan for monitoring and evaluating trainee's progress toward independence); e) environment and Institutional commitment to the candidate (assurance of 75% protected time, availability of appropriate research facilities, evidence of commitment to trainee's career development). Each trainee applicant will be interviewed by an experienced clinical/translational investigator to assess the applicant's potential for team research, focusing on the applicant's potential for participating in transdisciplinary investigation. A report of the interview will be provided to the review group.

Faculty from MCW, UWM, and MU are eligible for entry into the training program, and in the past, many departments have been represented, including medicine, pediatrics, surgery, otolaryngology, psychology, pharmacology, electrical engineering, obstetrics/gynecology, radiation oncology, physical therapy. Applicants accepted into the program also represent a wide range of departments. The rapidly expanding faculty of the UWM Zilber School of Public Health provides another pool of potential trainees for this program. As in the past, the following strategies will be used to recruit applicants to the program: a) letters to Department chairs at MCW and to the Deans of health professional schools at the other academic partners; b) repeated program announcements in bulletins of each of the partner institutions; c) email notification sent to approximately 1,500 CTSI members at the various partner institutions; d) discussion of the program with previous and current clinical scholars (K30); e) scheduled group sessions for potential applicants that briefly explain the program and the application process and answer questions; f) informal word of mouth.

Another asset of the training program is the provision of a supportive peer group of trainees. We have successfully leveraged NIH support to obtain institutional support for additional trainees. Programmatically, we make no distinction among trainees, based on their sources of support. Currently, five trainees are participating in the program, and all are concurrently active members of the larger Clinical Scholars Program. Either previous or concurrent participation in the Clinical Scholars Program is a requirement for all trainees. Additionally, former scholars and trainees have begun mentoring current clinical scholars by giving talks to the entire group and by participating in small group discussions that may be related to career development or review of a scholar's draft of a manuscript or grant application. Perhaps most importantly, successful former scholars serve as role models for their successors in the program.

MCW has 7-T32 awards (Medical Science Training Program, Vision Science, Integrated Physiology, Inflammtion & Infection in Acquired and Congenital Cardiovascular Disease, Anesthesiology, HIV Prevention, and Hypertension & Vascular Biology), 2-T35 awards (Medical Student Summer Research Training and Medical Student Training in Aging &Injury Research) and 2-R25 NIH-funded research training and research education programs in 2014. In addition, the current CTSA application includes a request for research training of 10 pre and/or post doctoral students (TL1). Candidates for the TL1 award include pre-doctoral MD and PhD candidates (including MSTP candidates), as well as post-doctoral clinically trained fellows. We propose to create a "K-T Forum" to invite all T awardees, former and current trainees in the clinical research training program, and faculty who have individual K awards from NIH. At MCW there are currently five K08 awardees, two K23 awardees, two K01 awardees, and one K99 awardee. At UWM and MU, there are 4 and 3 individual K awardees, respectively. The primary function of the Forum will be to assist its members in becoming imbedded in a multidisciplinary research team. Trainees will be encouraged to present their work-in-progress. As suggested by our former clinical research scholars, the Forum also will be a resource for individual trainees to share their career development plans and concerns with peers. It will also provide an opportunity to share and critique research plans, and drafts of grant applications and manuscripts. The Forum will meet monthly on a regularly scheduled basis.