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PI: Michael W. Konstan, MD

Title: Clinical and Translational Science Collaborative of Cleveland

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SPECIFIC AIMS

Clinical and translational (C/T) research is essential to bring the discoveries of biomedical science to benefit the population of our nation, and to use our knowledge to improve human health. C/T research will inform the application of our knowledge to disadvantaged and other populations to improve overall health. In Cleveland, the need is dire because of infant mortality nearly three times the national average, and disparities in life expectancy of more than 20 years between inner city neighborhoods and a suburban site only eight miles away. These health disparity statistics are replicated at other sites across the country, so we may be a model for this need. C/T research will help develop and test the new drugs to conquer cancer, Alzheimer's and other neurodegenerative disease, as well as genetic disorders, and even the common cold. Potential therapies are now incubating in our basic science laboratories and will soon come to clinical testing. However, numerous barriers now exist to efficient execution of C/T research. We developed the Clinical and Translational Science Collaborative (CTSC) in 2007 to 1) identify and systematically surmount these barriers, 2) accelerate the movement of discoveries to patients, and 3) apply C/T knowledge to improve human health. Success in C/T research depends on a steady supply of superbly trained C/T investigators at all levels to comprise a flexible and nimble workforce, which the CTSC is proud to educate. **We aspire to be a catalyst for high-quality C/T research, both locally and nationally.**

As we describe below, the major educational and healthcare institutions in our city, as well as biotechnology companies, government agencies, and community agencies, collaborate through the CTSC to reach these goals and to develop a system of C/T research to the highest possible standard. Each partner contributes in a unique way to the whole, while participating in the activities that constitute the fundamental basis of the Hub. Our partner hospital systems each bring special expertise and populations to the consortium, and all four contribute dedicated C/T research facilities and support for the pilot programs of the CTSC. We have created a solid foundation on which to build our vision to utilize the power of this collaborative to ensure rigorous and innovative training of the C/T workforce, to accelerate the translation of discoveries to patients, and to improve the health of Cleveland and provide scalable models for other locations throughout the nation.

To achieve these goals, we will execute the following **specific aims**:

Aim 1: **Engage** all C/T science stakeholders, the workforce, patients and community members to **collaborate** locally, regionally, and nationally, to advance human health.

Aim 2: Develop and cultivate the current and next generation **C/T research workforce**, with special focus on preparation for team science and increasing the diversity of the workforce.

Aim 3: Promote integration of our translational processes from discovery through clinical trials, of our community throughout the research enterprise, and of special and underserved populations into C/T research across the lifespan.

Aim 4: Increase the quality and efficiency of C/T research, particularly multi-site trials, through **innovative methods and processes** and strong collaboration among CTSC Hubs.

Aim 5: Provide **innovative informatics** to support the training and research environment both in the CTSC and nationally.

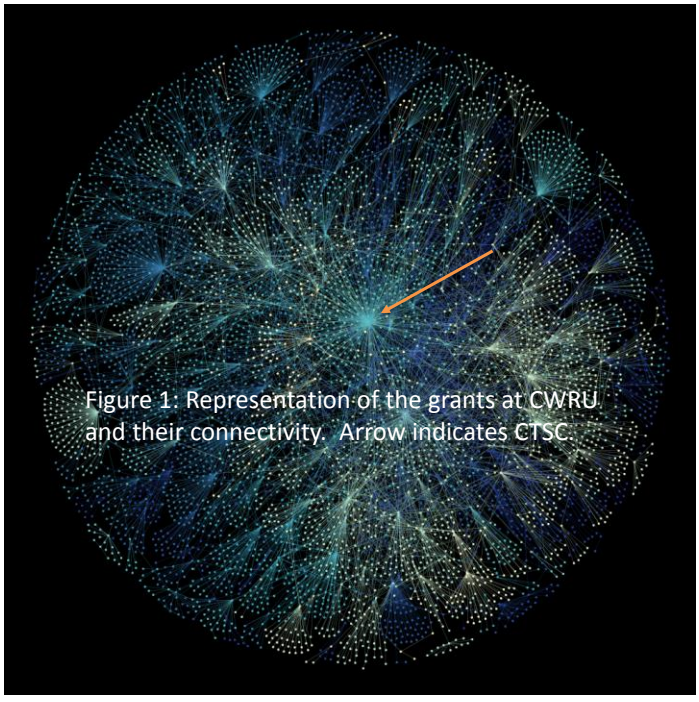


Figure 1: Representation of the grants at CWRU and their connectivity. Arrow indicates CTSC.

Over the last decade we have increased collaboration among the CTSC partners and developed resources and operations that lay a strong foundation for executing these aims. Moreover, the CTSC has emerged as a central feature of research at CWRU and its affiliated hospitals. Figure 1 illustrates the centrality the CTSC has assumed in the universe of grants at Case Western Reserve University (all NIH grants at all affiliates plus all grants in CWRU, University Hospitals Health System (UH), and the Veterans Administration Medical Center (VA), over 10,000 individual projects). This section will describe the strong base on which we will build the new iteration of the CTSC, and how we will implement the specific aims.

AIM 1: COLLABORATION AND ENGAGEMENT

Institutional Engagement and Collaboration: We have built a highly integrated and collaborative enterprise that has developed and disseminated innovative methods to enhance C/T research, and is poised not only to improve the health of Cleveland but also to bring more new therapeutics, IT innovations, and devices to general use. We are confident that we can advance toward these goals because solid progress has occurred over the last decade. The CTSC is anchored at CWRU, which has multiple health sciences schools and is affiliated with all four major hospital systems in Cleveland. Although the bulk of the CTSC occurs in the School of Medicine (SOM), all eight Schools participate. The Collaborative includes four hospital partners: the Cleveland Clinic (CC), a *USNWR* honor roll hospital and an international leader in clinical innovation; MetroHealth System (MH), a county-supported public safety net hospital that was awarded the HIMSS Davies Award for outstanding utilization of health IT to substantially improve patient care while achieving return on investment; University Hospitals (UH), a classic academic medical center that won the McKesson Quality Award four years ago; and the Louis Stokes VAMC (VA), one of the top VAMCs in the nation in all measured categories. Each system has a distinct mission, separate board of trustees, and independent governance. They compete clinically, but each brings distinct strengths to the collaborative**.** Together, these hospital systems care for about 90% of the population in the eight-county Cleveland area. **In many ways, our CTSC is a microcosm of the national CTSA consortium, for we have had to establish mechanisms for effective collaboration among partners with different priorities, governance, and technical capacity.** The CTSC does not have line authority over all its participants, but in the end all collaborative research occurs as a "coalition of the willing". The CTSC facilitates studies and provides efficient services for the participants who are then enabled to conduct research more effectively and are thus incentivized to participate. In addition to the institutional partners, we have engaged biotechnology and CRO companies to participate in the collaborative, particularly to provide trainee experiences in the private sector, and in our community research have engaged public health agencies and community organizations to address the complex problems of an urban environment afflicted with poverty and high incidence of chronic diseases.

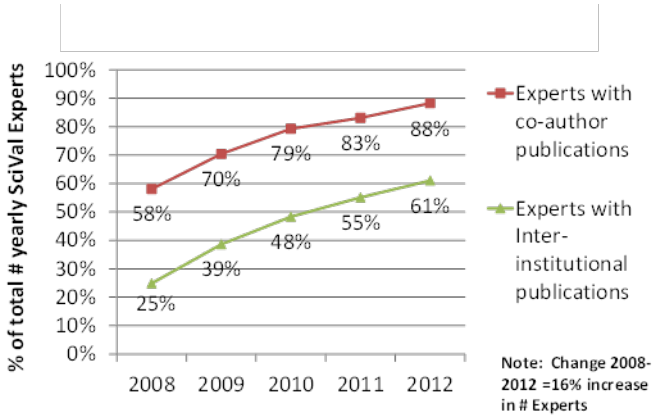


Figure 2: Collaborative publications among CTSC investigators increased over time, both coauthored publications and those with coauthors from different participating institutions. Data shown from SciVal Experts. In 2012 Sci Val Experts converted to PURE Experts, and the calculations for this topic are not comparable to the earlier calculations.

Institutional engagement is fostered by inclusion on the leadership team. The PI/Associate PI group consists of investigators from CWRU, UH, and CC. The leadership team of the KL2 and TL1 consists of investigators from CC, CWRU including the School of Nursing, and UH. The Executive Committee contains members from UH, CC, MH, VA, CWRU. Internal and external advisory committees contain, besides faculty from all participating academic/health care institutions, members from industry, the Cuyahoga County Board of Health, and patients.

Stakeholder engagement and collaboration: Since its inception in 2007, the CTSC has encouraged collaboration among institutional and external stakeholders. We established a superstructure, a web site, newsletters, meetings, an executive committee, core meetings, and points of contact for investigators –a concierge and an executive director. We encouraged use of CTSC cores by providing core utilization pilot grants, and incentivized collaboration by targeting pilot grants to collaborative ventures. We developed shared facilities so that investigators would interact around the science. We deployed SciVal® Experts (now Pure Experts) to help investigators find collaborators. Through all these mechanisms, as well as conscious efforts at culture shift, **collaborations increased, including those that span the city.** The proportion of investigators with publications with authors from different CTSC institutions increased more than twofold in four years, when the number of investigators increased by only 16% (Fig 2). CTSC emerged as a critical hub and information exchange for our biomedical community (Fig.1). We also include investigators from biotech, public health agencies, and the community at large in various aspects of the CTSC.

The CTSC has encouraged highly collaborative C/T sciences. For example, we increased the proportion of P and U grants (most of which are inter-institutional) in our portfolio: between FY13 and FY16, such grants increased from 23% to 28% of the portfolio. Examples are a SPORE grant in GI cancers, the inflammatory bowel disease consortium (anchored by new P30, P01, T35 and T32 grants), the National Center for Advancing Innovation (NCAI) (U54 from NHLBI), StrokeNET (U10 from NINDS), and two new P01s on airway biology (CC and UH/CWRU). Spanning the institutions is the Institute for Computational Biology, for which we recruited a Director and faculty using pooled funds from CWRU, CC, and UH (not from the CTSC). This program now anchors informatics in the CTSC and CTSC makes its resources available citywide. A program in Autism, headed by the Deputy Provost at CWRU, extends citywide and has received funding from local foundations and at the national level. It is not CTSC-supported directly, but the citywide alliance facilitated by the CTSC provides shared resources and underpins these collaborations. In addition, all these programs, though paid through institutional funds and other grants, used CTSC resources, such as the CRUs, REDCap, statistical support services, or core facilities. **The CTSC emerged as a driver for expanding and integrating research across the city and is a central feature of the Cleveland/CWRU biomedical ecosystem.**

We aligned the academic reward system to support team science. In 2006, the SOM changed its bylaws to explicitly recognize team science as a pathway to promotion and tenure. From FY09 through FY16, 115 of 119 (96%) applicants for promotion (tenure and non-tenure tracks) who identified themselves as team scientists were promoted. For tenure, 44 of 49 (90%) of team science based applicants received tenure. (CC does not allow tenure). The Case School of Engineering, Frances Payne Bolton School of Nursing, and Mandel School of Applied Social Sciences now also credit team science in the promotion process. Our KL2 and TL1 programs provide explicit instruction in team building and maintenance.

Collaboration has also been encouraged by maintaining and consolidating, where appropriate, excellent core facilities across the city, to allow investigators not only access to technical help, but also intellectual exchange. Core facilities were established (e.g., genomics, bioinformatics, high throughput screening – all equipped with institutional funds), consolidated (e.g., two monoclonal antibody facilities consolidated to one at CC, three transgenic/knockout mouse facilities consolidated at SOM) or strengthened. We connected the shared facilities from CTSC and the CCCC and adopted best practices wherever they were developed. High-end core facilities, such as induced pluripotent stem cell facility, GMP stem cell production facility, imaging, proteomics, and informatics, encourage intellectual collisions of investigators at different institutions and in different areas, leading to collaborations. All core facilities provide training to assist users. All are continuously monitored for utilization and quality of service and output.

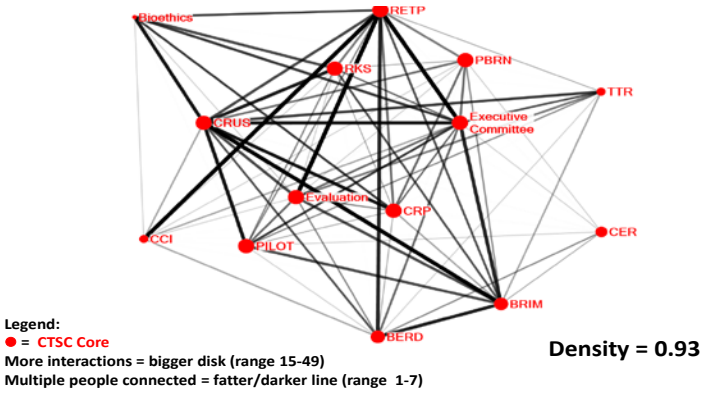


Figure 3: Core-Core Interactions in the CTSC

The core directors, both from the CTSC and from other entities, in 2014 developed a grassroots effort to come together to meet regularly, hold an annual symposium, and address common issues. This collaboration led to a common billing system, sharing of administrative resources, consolidation of small cores into larger entities, and exchange of ideas. This grassroots effort reflects effective communication among CTSC cores, indicated in social network analysis (Fig 3), where the measure of connection, density, was 0.93 (maximum possible value of 1.0). Such communication allows investigators to move easily from the preclinical to the clinical space. In general, the **community of C/T scientists is aware of the resources available to them, and eager to collaborate to accelerate progress.** We track core interactions to identify and disseminate best processes as well as areas that are slower to improve.

Engaging the medical community in research collaboration: To achieve our goal of improving the health of the community, we collaborate both with the physicians in the community and with the citizens living and working in it. Our region has a long, distinguished history of collaboration and integration of community and academic physicians engaged in primary care in our Practice Based Research Networks (PBRNs). Established networks derive about half their research projects from community physicians, and half from the academic collaborators. With stable support from the CTSC, the PBRN model was extended to dermatologists, dentists, and nurse-practitioners. The well-developed primary care PBRNs connected across Ohio in an AHRQ-funded network.

Funding from the CTSC, used judiciously by Kurt Stange, MD and James Werner, PhD has been catalytic in creating these new network connections. Our PBRNs have had substantial influence on mechanisms of delivery of primary care, on process and outcome for common conditions, and on closing the racial and socioeconomic health gap in Cleveland, and they continue to create learning health communities (see Integration section below).

Engaging the community at large in research collaboration: We have had strong integration of CTSC-related research with the community, at the level of community agencies, public health departments, and the community at large. Our programs involve a multipronged approach of respectful collaboration, education of community representatives as research drivers, and now has expanded to two large projects which have engaged large segments of the community in deciding the specific areas of focus, followed by implementation and evaluation of the programs (Health Improvement Plan-Cuyahoga and First Year Cleveland, see below). Many of our methods are transferable and scalable in communities that resemble ours. We also engage minority communities in our C/T research and have contributed discoveries that may change our approach to health care for hypertension and colon cancer in the African-American community (see below).

Earlier iterations of the Community Research Partnership (CRP) cores of the CTSC, as well as our Prevention Research Center for Healthy Neighborhoods from the Centers for Disease Control (PI Elaine Borawski, PhD), and the NIH-funded Center for Reducing Health Disparities (PI Ashwini Sehgal, MD) developed ties with community groups and members over a decade. Drs. Borawski and Sehgal head the CRP Core of our current CTSC. To increase understanding of our community by academics, we trained 252 academics in cultural competencies, and toured the neighborhoods with 74 investigators. To increase community capacity for research, we qualified 52 community members to be investigators on IRB protocols. More in-depth training of community members is conducted in the Community Research Scholars Initiative (CRSI), a two year intensive training program that aims to increase research and evaluation skills and to create a Community Research Network. Scholars came from a broad range of community agencies, such as YMCA, LGBT Community Center, Asia Services in Action, Massage of Northern Ohio Practice-Based Research Network, and others. As the initial cohorts completed the program, the Community Based Research Network (CBRN) was established, which is now exploring a joint evaluation project aimed at increasing community research capacity.

In addition, to improve the ability of community organizations to participate in research and to facilitate academic/community research partnerships, we created Partners in Education, Evaluation and Research (PEER), a 15-month, part-time mentored program. PEER creates *research triads* within the organization comprised of a Fellow, an organizational mentor (usually the supervisor of the Fellow), and a compatible faculty member. Nine months of didactic seminars (56 hours) and six months of independent fellow/faculty partner research work culminate in presentation at a community/campus forum. Fellows came from the Cuyahoga County Board of Health (CCBH), Care Alliance, Center for Cognition and Recovery, Educational Services Center of Cuyahoga County, Cleveland Rape Crisis Center, the Cleveland Regional Perinatal Network, Cuyahoga County Planning Commission, The Gathering Place, Healthy Fathering Collaborative, Hunger Network, and Neighborhood Family Practice. One example of success is that the PEER team at CCBH wrote and received a grant of $4M from DHHS, Office of Adolescent Health, to provide evidence based sexuality programming in the Cleveland public schools. Thus, community agencies are integrated into the research continuum. We will continue all of these educational activities in order to continue to build capacity for community-based research.

In collaboration with public health and other agencies, members of the CTSC have been active participants in a countywide plan to improve health, called **Health Improvement Plan - Cuyahoga (HIP-C),** a consortium of three area public health departments and more than 100 organizations, including the hospitals and academic units engaged in the CTSC. HIP-C spent two years engaging in the community to select four consensus areas of emphasis. A CWRU faculty member co-leads HIP-C with a community representative, and two of the four working groups are headed by CWRU faculty. Community agencies garnered over $13M in external grants to support HIP-C, all of which include a university or CTSC-based evaluation component. This highly integrated model has already demonstrated tangible progress in three of the four areas selected for emphasis: 1) eliminating structural racism; 2) healthy eating, active living (headed by a faculty member in our Prevention Research Center, which grew from the original community research partnership core in the CTSC, which, for example, partnered with the YMCA to train middle school students in running in “We Run This City”, a pre-marathon training program that reduced the prevalence of hypertension by more than 50%) 3) chronic disease management (headed by a staff member of Better Health Partnership, a CTSC-supported PBRN, based on its successful strategies detailed below under Integration) and 4) connecting clinical care with public health (headed by a CWRU faculty member embedded in the Cuyahoga County Board of Health). The Steering Committee of HIP-C includes CTSC faculty. HIP-C represents a strong collaboration between the CTSC, the university and the community.

CTSC-affiliated faculty from our Urban Health Initiative and Prevention Research Center were instrumental in creating the County's first early childhood wellness plan through a coalition through the County Board of Health. CWRU developed RaisingHealthyKidz.org to provide vetted resources to support parents and child care givers in improving nutrition and physical activity policies and practices. Similar to HIP-C, our faculty have built relationships of trust with community and governmental organizations focused on maternal and child health, which will facilitate research in women and children and assist in **First Year Cleveland (FYC)**, a City of Cleveland initiative, aimed at improving the dismal city record of infant mortality by "improving care, promoting safe sleep measures, centering pregnancy, and community engagement". The CTSC PI, Michael Konstan, MD, leads this initiative. This program will call upon CTSC as well as community resources. HIP-C and First Year Cleveland constitute some of the platforms for novel C/T research that we will build and maintain.

We have also integrated the laboratory with the community in part through the CTSC. Jackson Wright, MD, PhD, former CRU director, was the lead investigator on the hypertension study SPRINT, which was stopped early in 2015 because of the overwhelming benefits of tight control of blood pressure.[(1)] He is a widely emulated leader in the US in recruiting and retaining African-American participants in clinical trials. His attention now turns to disseminating and implementing the results of this critical trial. Sanford Markowitz, MD and his team discovered that the genomic mutations identified in colon cancers from African-American patients differ from those in white patients,[(2)] suggesting a biologic basis for the increased severity of these cancers in the African-American population, providing potentially drug-able targets, and extending precision medicine to the African-American community for these cancers.

Involvement of patients in CTSC: We include patients and family stakeholders in CTSC activities. In fact, some organizations that have participated in our research projects are largely composed of patients (e.g., The Gathering Place, cancer survivors; Center for Cognition and Recovery, dementia caregivers; LGBT Community Center, HIV patients, to name a few). We engage patients in our advisory panels, including internal and external advisory committees (see *Administrative Core*). The Child Health Advisory Board contains parents, and the Translational Workforce Development Advisory Board and the Scientific Review Committee have patients as members. The perspective of the ultimate consumer is crucial in planning and evaluation of our programs.

Collaboration and engagement with CTSA Hubs - Commitment to Innovation in Clinical Research: CTSC places high priority on improving the efficiency and management of clinical trials by extending our management approach to the multisite trials that we perform with the CTSA Network, providing the CTSA Network with strong support and established leaders in multi-site, NIH-supported clinical trials and by subscribing to its plans to provide central IRBs and pre-negotiated subcontracts**. CTSC has great enthusiasm for inter-Hub collaboration and looks forward to sharing best practices through RICs and TICs.** Indeed, our 3-Hub Ohio Clinical Trials Collaborative (OCTC) (Cincinnati, Ohio State University, and Cleveland), formerly led by James Chmiel, MD, developed successful processes for the efficient management of multi-site trials and applied continuous quality improvement principles to maximize efficiency and performance. Systems are in place that provide scalable prototypes for enlarged systems that could work on a national level. Our reliant IRB model was one of those that ultimately evolved into the SMART IRB to which we all subscribe. A resource for subject recruitment and public connection to ResearchMatch is maintained in a web site (Netwellness.com, 1.4M hits/month) supported by the three Ohio CTSAs. Our statewide collaboration led to a funded grant from NHLBI based at CC to support translation to clinical testing of basic discoveries in the heart, lung, and blood space (NCAI). The former OCTC leader (James Chmiel, MD) is now one of our liaisons to the TIN, (along with Lara Jehi, MD, one of the leaders of the CRU at the CC) and makes the same commitment to collaborate and innovate within the CTSA network.

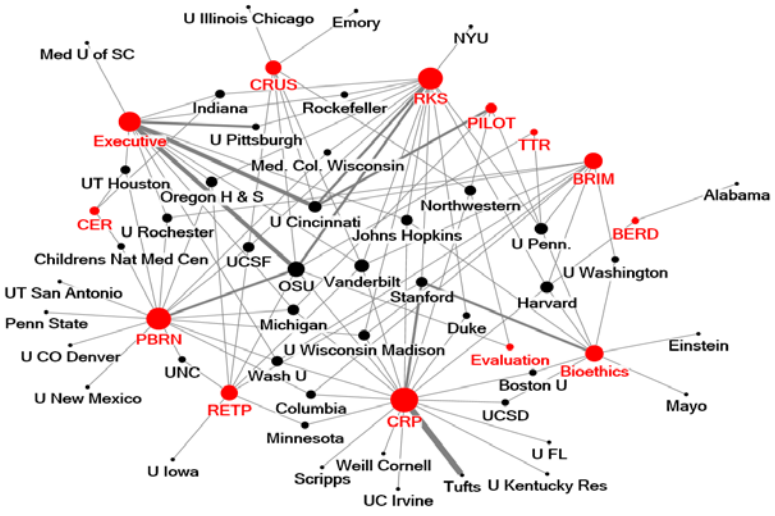


Figure 4: Connections of CTSC Cores to other CTSA hubs, 2015.

Besides our participation in the GCP standardization project and IRBRely, we have adopted REDCap and ResearchMatch and become major users. For example, over the last five years,

CSTC support resulted in a 260% increase in REDCap users to over 950, and a twofold increase in REDCap projects to over 850. We are implementing i2b2 and SHRINE as a federated approach to data management. We distributed our own informatics tools from GQ Zhang, PhD (Former informatics co-director) and his team that harmonize data collection from different instrumentation devices in sleep and epilepsy. Individual connections through our CTSC Cores are abundant, as shown in Figure 4. *Regulatory Knowledge and Support (RKS)* has many connections as we "go national" with common IRBs; our PBRNs, some of the oldest and best-published in the US, have contact with many other sites across the state and beyond.

Our Hub has been active in national multi-site clinical trials which include other CTSA Hubs, and leads several of them (Table 1). Some current trials are the descendants of earlier trials: e.g., in hypertension, we began with ALLHAT and followed with SPRINT. In diabetes, we led the DCCT and now lead EDIC and TODAY, sometimes with several generations of investigators. This longstanding commitment to clinical investigation persists today.

Table 1: National Clinical Trials led by CTSC Investigators

Study	PI	Topic	CTSC Use	Funding
CF Clinical studies	Michael Konstan MD, **CTSC PI**	All new drugs for CF	CRU, Informatics	NIH, CF Fndn, Industry
SPRINT (Also ALLHAT, CRIC et al)	Jackson Wright MD PhD, **former CTSC CRU lead**	Hypertension, esp in African Americans	CRU, Informatics	NIH 268200900049C-14-0-1
SUDEP	Samden Lhatoo MD, PI. GQ Zhang PhD and S. Sahoo, PhD, informatics	Sudden death in epilepsy	CRU, Informatics	NIH U01 NS090407
EDIC, TODAY (from DCCT)	Rose Gubitosi-Klug MD PhD	Diabetes control	CRU, Informatics	NIH U01 DK094157
StrokeNET	Anthony Furlan MD	Stroke therapy	CRU, Informatics	NIH U10 NS086532
Heart Failure Network	Wilson Tang MD, **CTSC CRU lead**	Heart Failure	CRU, Informatics	NIH U10 HL110336
NIAID new drugs, vaccines	Robert Salata MD	Novel anti-infectives	CRU, Informatics	NIH HHSN272201500007I

In addition to the trials we lead, we participate in Severe Asthma Research Program, Prevention and Research of Early Lung Injury, Alliance of Randomized Trials for Medicine vs. Metabolic Surgery for Type 2 Diabetes, Nonalcoholic Clinical Research Network, Neonatal Research Network, and Functional Connectivity in Premanifest Huntington Disease. We serve as the Clinical Center for the Cardiothoracic Surgical Trials Network, and the Clinical Research Skills Development program: we serve as data coordinating center for the Hemodialysis Fistula Maturation Consortium, the Pulmonary Vascular Disease Phenomics Program, and Pilot Studies of Candidate Therapies for Chronic Kidney Disease. Most of these include and are led by other CTSA Hubs. **We are both leaders and strong participants in the NIH's clinical trials program**.

AIM 2: WORKFORCE DEVELOPMENT

CTSC embraces a comprehensive approach to developing a workforce that includes a diverse assembly of highly competent investigators, fully integrated into CTSA-directed C/T research, and is also aimed at meeting a broad array of unmet health needs. Our vision, to be executed through the Translational Workforce Development module, is that all members of this workforce are specifically trained in skills needed to serve on and lead scientific teams, to approach the use of novel, complex tools and systems with skill and familiarity, based on training by relevant experts, and to demand of themselves high-level proficiency in Good Clinical Practice (GCP), regulatory knowledge, entrepreneurship, innovation, product development, basic science, implementation and community engagement in which they are trained by Core leaders at our institutions. The CTSC partners came together to create a Clinical Research Team Training Taskforce (CRTTT), to develop and implement training activities for investigators and research staff in the areas of Responsible Conduct of Research, GCP, and human-subjects research to complement offerings at each institutional partner. The CRTTT keeps abreast of the CTSA GCP supplement activities so CTSC partner institutions can integrate these products into their own individual training programs. Each institution has training programs in place for researchers at all levels which are augmented twice yearly by "umbrella" CRTTT programs. Workforce development will be augmented by a pilot grant program aimed at developing novel methodologies and solutions to national problems such as health disparities and special populations.

For many studies, it is important to engage community members as part of the research team, and to have the academic members of the team appropriately sensitive to the community's needs. As noted above, CTSC trained 270 academic investigators in cultural competency for various study populations. We also welcome community

members in the planning and execution of research protocols, and so trained 82 community members, most with no prior research experience, to achieve certification as approved investigators for IRB proposals.

Professional team leadership is critical, and education for such leadership takes place at many levels. We instituted a strong Clinical and Translational Scientist Training Program (CTSTP) in 2007, modeled on our highly successful MSTP template, which has been funded by NIH continuously for over 40 years. While MSTP is focused on laboratory basic research, CTSTP addresses areas critical for C/T research and provides the expanded didactic opportunities essential for students to grasp the sweep and rapid evolution of the field (for example, training in cultural competency, informatics, statistical methods, team building, crisis control, and project completion). Also, CTSTP creates a cohort not only of MD-PhD candidates, but also dental and nursing dual degree students who interact and learn together. To augment opportunities, we developed a PhD in Clinical and Translational Sciences (led by Li Li, himself an MD-PhD in epidemiology and a family physician) and another in Systems Biology and Informatics (led by Mark Chance, Associate-PI), both approved by the Ohio Board of Regents in the last five years. This program is young: of 17 MD-PhD graduates, 15 went to excellent residencies (12 still there), and two joined biotech firms. Five received achieved some grant support as residents or junior faculty. Three are junior faculty. For the DNP-PhD trainees, two are working in the areas of their research (flight nursing and underserved populations). We will now extend CTSTP training to the postdoctoral level. We will engage with our industry partners to instruct our investigators in industrial team management approaches. We have developed coursework in medical informatics that supports the Medical Informatics fellowship based at MH, and serves as the basis of a certificate and an MS in health informatics offered through our Department of Population and Quantitative Health Sciences, headed by Jonathan Haines PhD, lead of our CTSC *Informatics* component.

CWRU SOM requires all MD students, even those not enrolled for dual degrees, to write a thesis. Time allocated for research during the MD curriculum ranges from 26 (University track) to 52 weeks (Cleveland Clinic Lerner College Track), or more by arrangement. Many students with longer blocks seek the MS in Clinical Investigation, and we have enthusiasm for the nascent MS in medical informatics. Although these students are not supported by CTSC directly, they benefit from CTSC course development.

At the junior faculty level, KL2 Scholars have been educated in a formal program since 2004 (K12 which folded into the CTSA). Our goal has been to develop a cadre of C/T team scientists from diverse backgrounds with broad knowledge of the techniques and requirements of C/T research who are also steeped in the principles of leadership and team building. We also intended to reduce the time to independence: therefore, we planned a four-year program with the expectation that independent grant application (not another K award) will be written by the end of year three. The results have been gratifying. Average age at R, U, or other independent funding for our Scholars is 38 years for our program vs 42 for PhDs and 44 for MDs nationwide. Although grant funding cannot be the sole metric by which we judge this program, it is a *sine qua non* for continuing to work in clinical investigation. Over 70% of KL2 alumni have non-pilot, non-institutional independent funding by year five, with 40% having an R01, compared to 20% of K award investigators nationwide who obtain R01s. Two Scholars in one cohort teamed up to obtain an U01 grant, now extended to a new U01 to move into patients. This illustrates the importance of creating a cohort for support and intellectual interaction, and argues strongly for our proposal, to introduce a “K Club” of junior faculty who hold a K award or equivalent and who will utilize the didactic systems developed for the KL2 as well as the extensive monitoring of K award progress. More than 90% of the Scholars remain in academics or industry research. Those enrolled in the early cohorts have mostly been promoted to associate professor at least. One is now a department chair. We have admitted about 55% MD’s and 17% nurses, with engineers, genetic epidemiologists, a family therapist, and a dentist rounding out the cohort.

Workforce diversity: We intend to improve the representation of underrepresented minority (URM) investigators in C/T research, not only by seeking out and training such individuals in our current programs, but by establishing pipeline programs to bring such individuals into science and medicine. The need for URMs is especially severe at the doctoral level. CWRU is committed to creating an appropriate pipeline to increase the pool from which we select C/T investigators. The SOM and the School of Dental Medicine were longtime participants in the Summer Medical and Dental Enrichment Program (SMDEP) for URM undergraduates sponsored by the Robert Wood Johnson Foundation. We also have a pipeline program which extends from a Cleveland public high school of science through full scholarship at CWRU undergraduate to full scholarship at the School of Medicine (first matriculant 2016). To enhance the early pipeline, the SOM offers summer research programs to inner city students. Special scholarships for SOM and named clinical fellowships at UH aim to attract URM students. While no one would declare victory, our conscientious effort has modest success**. In our TL1 program, 14% of the students have been URMs. In the KL2 program, 12% of trainees are URMs, and 48% are women**.

AIM 3: INTEGRATION

We demonstrated examples of integration of the community with the academic research continuum, both in the realm of epidemiology and with laboratory science ("engaging the community at large…" above). Here we will discuss integration of research with health systems management as well as with the community. In addition, we will discuss integration of special populations into the research programs of the CTSC.

Integration of research with practice management systems through Practice Based Research Networks (PBRNs) (and integration of special populations into research): Our PBRNs have had profound impact on the systems of care now being tested in the United States. One of the earliest PBRNS, the Research Association of Practices (RAP), headed by Kurt Stange, MD, launched in 1994 with the Direct Observation of Primary Care (DOPC) Study (funded by NCI and the Robert Wood Johnson Foundation.). DOPC directly observed 4454 outpatient visits to 138 family physicians,[3,4] and through detailed analyses of rich quantitative and qualitative data (70 publications), produced new understanding of primary care. Amidst system pressures to simplify primary care to the management of single diseases, the DOPC study discovered that the competing demands[5-8] of integrating,[9,10] personalizing,[11-15] and prioritizing[16-21] care for whole people[22] and families,[23-26] are in fact the major strength of the primary care approach.[27-30] DOPC discoveries about how preventive care is integrated into real-world practice[31-37] led to the STEP-UP randomized trial of 80 practices that resulted in substantial, sustained improvements in delivery of evidence-based clinical preventive services.[38] This research gave novel insights into the process of facilitating practice change,[38-48] and led to the country's first national demonstration and evaluation of the patient-centered medical home (PCMH),[49-55] now widely touted to improve care and control cost.

STEP-UP findings and intervention methods were extended to the Rainbow Pediatric PBRN in Cleveland in a clinical trial that produced large effect sizes in improving child preventive service delivery.[56] These data were used to support a successful application for a CMS Innovations grant that institutionalized and expanded the facilitation practice improvement approach in a pediatric Accountable Care Organization. This program integrates children of lower socioeconomic status into viable care plans to deliver preventative care and identify routes into the medical system. Thus, over two decades, PBRN-based studies, led by Kurt Stange, MD and James Werner, PhD, have impacted care delivery in Cleveland and beyond. The stability of infrastructure funding provided by the CTSC to the PBRNs allowed the primary care PBRNs to extend their reach into a statewide network funded by AHRQ, and allowed established PBRNs to assist in development of new PBRNs in other disciplines.

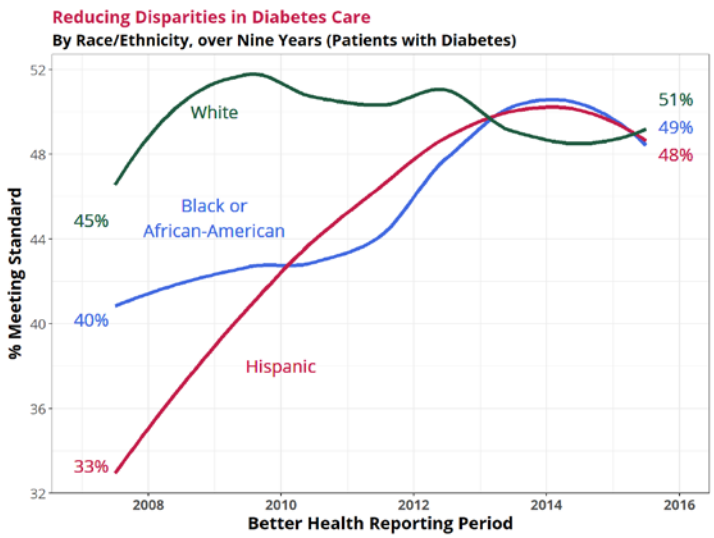


Figure 5: Reduction in disparities in diabetes care over a 9 year period in primary care practices in the Better Health Partnership.

One especially effective PBRN is the Better Health Partnership (BHP) led by Randy Cebul, MD, the evaluation arm of which is supported in part by the CTSC. BHP, with more than 80 primary care practices, is also an example of a learning health system. All practices report their data on Type 2 diabetes, hypertension, and heart failure, and the results of process and outcome are posted on the public BHP website. Data analytics identify the top-performing practices. Elements of success are identified, then tested at poorer performing practices, and if validated, are disseminated to the entire group as "best practices", where adoption throughout the network results in overall improvement. Initially, patients of low socioeconomic status (SES) posted worse results, and racial disparities were evident. Over the first three years, all practices except one improved in process, outcome, or both, and HgbA1c in ~27,000 Type 2 diabetics dropped by one percentage point, enough to predict fewer complications. Practices with EHRs performed better and improved more than those without EHRs. [57] Nine-year follow-up data now indicate that the racial gap is closing. (Figure 5) This remarkable integration of patients of low SES into research protocols has resulted in substantial improvements in care processes and outcomes. This strategy is being adopted statewide in a cardiovascular disease prevention program sponsored by the state, including the other CTSAs in Ohio, and led by CTSC PI

Michael Konstan: the goal of reduction of high blood pressure is pursued with the end expectation of reducing downstream complications of stroke and heart disease. BHP is now recruiting pediatric practices to focus on pediatric asthma and childhood obesity, consonant with the CTSC emphasis on pediatrics, and integrating the pediatric population into this highly successful model.

MH compared patients in a Medicaid managed care program managed with BHP strategies with those not continuously insured. There were only somewhat better outcomes in the managed group, especially for the three target conditions, but costs were 28% below the state-capitated rate for those managed with BHP principles, an unexpected finding after the Oregon experiment which only compared patients covered by Medicaid with those who were not[58,59] and found that insured patients cost more. The MH experiment presages the new wave of quality improvement clinical investigations that will integrate with health systems to improve care at lower cost, and focuses on underserved populations. Such experiments break new ground in health systems research, and provide scalable models for expansion.

Integration of research with clinical protocols to improve patient care: Use of continuous monitoring as occurs in the intensive care unit produces volumes of data that are often discarded. At CC, all intensive care monitoring from all its hospitals feed into a single site. CTSC *BERD* developed an algorithm with high predictive value to identify high acuity states. Application of this algorithm combined with EHR alerts to the nursing staff reduced the time patients spent in "high-acuity" states by 36%. The project is now progressing to predict cardiac arrest. Another example is the identification in the CC system of variable use of transfusion following orthopedic procedures. The informatics team analyzed system-wide data and developed an algorithm to predict optimal criteria for blood transfusion. Following introduction of the algorithm and EHR alert in one non-central hospital, transfusions fell by more than 80%.

Integration of special populations into studies: CTSC works across the lifespan. The SPRINT trial, led by Jackson Wright, MD, PhD, who directed the CTSC CRU at UH, is an excellent example of integration of elderly populations into clinical trials. About one third of the patients were over 75 years of age, because the critical clinical question was whether aggressive lowering of blood pressure in the elderly would result in adverse outcomes.[1] Wright's life work is an excellent example of recruitment and retention of African-American participants into clinical trials.[60,61] His strategies of working through community leaders, especially the churches, as well as establishing health care facilities in the neighborhoods that contain clinical research facilities and engaging town practices, are now widely imitated and have proven durable in the Cleveland community. African Americans are the most numerous under-represented minority in Cleveland, but a substantial Hispanic community lives in Cleveland as well. To assure their integration into clinical trials, we offer coursework in medical Spanish. More than 140 learners at four levels are now enrolled. In addition, our CTSC Community Engagement core offers Spanish translation services both on-the-spot and for consent forms and information sheets for clinical trials, because hospital-based translators must give priority to clinical services. In the SPRINT trial, about 10% of the participants were Hispanic, close to the proportion in the population.

We have addressed serious health problems in the pediatric population as well. In addition to many clinical trials in cystic fibrosis, obesity, and diabetes (see Table for some), CTSC joined a statewide program to identify the causes of prematurity, supported by the March of Dimes. To further the goal of reducing infant mortality in Cleveland (currently a dismal 13 per 1000), we became the home base for First Year Cleveland (led by CTSC PI Michael Konstan), a City Council initiative. (See also section on "engaging the community…" above).

Integration of the community and research: The web site NetWellness was founded to provide nonbiased, non-commercial web based health advice for the State of Ohio. When state support ended, the three Ohio CTSAs took it over, and our CTSC improved the capacity to respond to queries by use of informatics tools[62,63] and we added a substantial section on clinical research – principles and practice of clinical research plus availability of clinical trials. NetWellness features topics coordinated with our local public television station (usually six 30-min programs) such as childhood obesity and environmental influences on the development of cancer. Improving public perception of clinical research will be important as our partner hospitals move to requesting broad consent to include clinical data and specimens in research programs. Moreover, this website may be the initial introduction to specific clinical trials in progress in our institutions.

AIM 4: PROCESSES AND METHODS

Accelerating discoveries from laboratory to patients: A major goal of our CTSC is to promote the translation of the discoveries in our laboratories to benefit patients. Mark Chance, PhD, Associate-PI of the CTSC, spearheads a thoughtful, accelerated process for development of nascent technologies and drugs (Figure 6).

Our innovative discovery research may suggest possible therapeutic targets or pathways, but defining a "drugable" target and identifying a lead drug compound is prerequisite for human translation. This process requires an integrated, well-coordinated system of cores for target definition and drug identification, with not only top-flight equipment but also expert consultation: structural biology, high throughput screening, medicinal chemistry, genomics and proteomics, all help to identify and design candidate therapeutic targets and drugs. We built and integrated these facilities and consultative services so that projects can be effectively managed through these cores. Since we have a strong stem cell program, we also developed a GMP cell preparation facility to produce stem cell therapeutics for clinical use. Finally, since the ultimate requirement is that therapeutics be effective in humans, projects need the opportunity to move into clinical trials. Sometimes at Phase 1 or 2, but certainly at Phase 3, the cost requires the engagement of industry, and at this point, projects often stall. Drugs and biologics in particular are viewed as high-risk.

To address this problem, we added an innovative component, two Translational Officers (supported in part by CTSC), recruited from industry. They review the research portfolio, identify discoveries that are ripe to be translated to human benefit, then work with the investigator to refine the studies' translational potential and "de-risk" them. If the discovery has promise, the Translational Officer helps the investigator present the technology to our Council to Advance Human Health, composed of experts from industry, patent law, and venture capital communities. They recommend university investment (or not) in the nonprofit space (made through a fund replenished by either philanthropic contributions, or in the case of NCAI technologies, from NHLBI, or in the case of projects from biomedical engineering, from the Coulter program). Their recommendations often include critical "killer" experiments that must be navigated successfully in order for the project to advance. Recommendations also include a tentative map to exit for the project, which may anticipate formation of a spinout company or licensing. The specific target exit often influences the details of the recommended experiments. Translational Officers serve as project managers, ensure that the investment is utilized as directed, and keep the project on track.

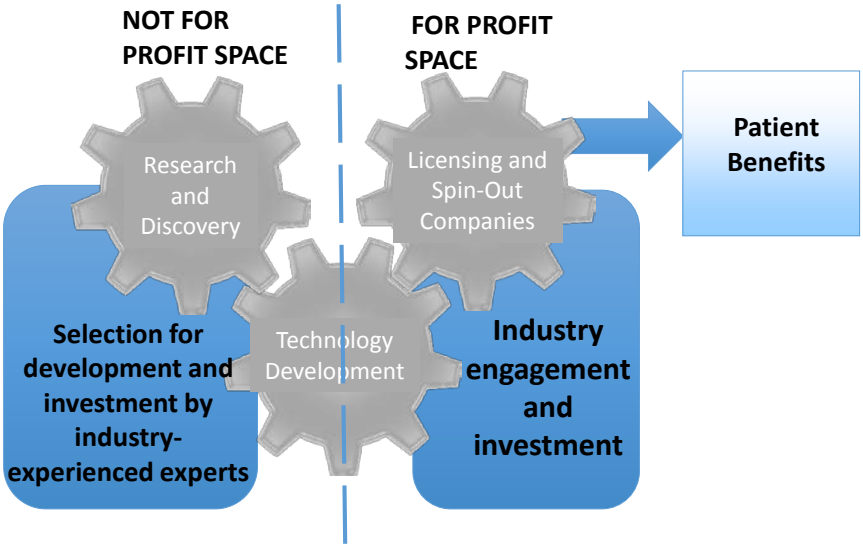


Figure 6: Planned progress of discovery research to patient benefit.

Examples of successful application of this process follow. A repurposed drug for Alzheimer disease [64] has come to clinical trials. A peptide for cancer detection[65,66] was paired with our magnetic resonance fingerprinting discoveries in imaging[67,68] for further investigation in animal models, garnered new NCI funding to improve sensitivity of cancer detection by 3 logs, and now is in line to receive NCI support for an academic-industrial partnership grant to continue development. A peptide treatment for spinal cord injury[69] is moving toward licensing and has also been successfully applied to limit damage from myocardial infarction.[70] A drug to accelerate bone marrow engraftment during transplant [71] is coming to licensing and clinical trial. An innovative approach to drug discovery in multiple sclerosis identified a combination of two repurposed drugs that in vitro increase new production of myelin received venture investment for the platform technology.[72] A portable device for rapid magnetometric detection of malaria [73] was licensed for production and distribution – and won the Patents for Humanity award. Our innovative project management strategies that either confirm potential and de-risk a project for for-profit investors, or fail fast, allow many more of our faculty's discoveries the opportunity to reach patients. Clearly, the cost of this program far exceeds the capacity of the CTSA to cover, but the CTSC provides support to a vital component of the ecosystem, the Translational Officers; the CTSC cross-state connections facilitated the competitive position of the National Center for Advancing Innovation from NHLBI, which supports some of the projects; CTSC-supported core facilities advance the preclinical and the clinical components; and the pivotal role of Associate PI Chance in these activities all indicate the crucial role of the CTSA in this translational program.

Two of the Associate-PIs (Dr. Davis and Dr. Chance) sit on the Board of Directors of BioEnterprise, a local nonprofit devoted to developing biotech in the for-profit sector in Cleveland, thereby connecting CTSC with the broader biotech community, the resources of BioEnterprise (such as inexpensive space rental, access to CEOs

in residence for part-time management, and access to funders), as well as local and statewide policy on biotech development.

Facilitating clinical trials: To accelerate initiation of clinical trials, CTSC developed a support structure for IND/IDE submissions that served 18 and 24 projects each of the last two years. Investigators can delegate the entire process to the core, or simply receive advice. We have also identified and developed strategies to surmount the barriers to rapid consummation of clinical trials, such as adequacy of the participant pool, IRB and contracting delays (often at multiple sites) and the ability to enroll subjects expeditiously.

Strategies for rapid identification of research subjects via EHR informatics help assure that there is an adequate pool of participants available and also to begin the recruitment process. Explorys, a CC spinout company now owned by IBM and incorporated into Watson Health, is a platform that allows such rapid identification, and is deployed at all hospitals affiliated with the CTSC except the VA. This platform has seen expanded use in the last four years, with over 8,000 queries. It grew out of eResearch, developed at CC, to serve three main purposes. First, eResearch/Explorys can survey the population with exclusion and inclusion criteria for a study and report how many eligible participants there are (criteria can then be tweaked to see if availability changes). Second, once a study is approved, eResearch sends an EHR alert so that all physicians who come in contact with a patient can discuss the study: if the patient is interested, a single click summons the study coordinator on the spot. Third, once the study has begun, eResearch scoops the relevant data to a research database from the EHR. The program is effective: for the Severe Asthma Research Program, eResearch was used to help identify and enroll 93 children in an H1N1 influenza vaccine trial during the same time period as the entire rest of the network enrolled 24 participants. Moreover, among about 800 participants identified by eResearch for a variety of studies, compared to those identified by hand, there were more African Americans (23% vs 5%, $P<0.001$), improving the diversity of the participant pool.[74]

Another point of delay is IRB approval, especially for multisite studies. We created a reliant IRB system first across Cleveland, then expanded statewide to other CTSAs (OSU and UC), improving final multisite approval to 16 days after initial approval. Our hospitals agreed to use common contracting whenever possible, though more work remains to smooth the process. In order to make clinical sites convenient, CTSC set up satellite units in the inner city, in addition to in- and out-patient facilities at the main campuses of CC, MH, and UH. Also, as needed, CTSC sets up recruitment and examination sites at borrowed facilities (churches, firehouses, and malls).

Results of process improvements: Our CTSC fares well compared to national standards. CWRU stands third in the country among academic institutions in the percentage of clinical trials listed on clinicaltrials.gov that show published results within two years,[75] with 44% published v. the national average of 29%. Another example is the work of the PI, Michael Konstan. His CF Clinical Research Center stood consistently in the top five nationally for such metrics as time from national opening of the trial to enrollment of the first subject, a composite measure of efficiency of recruitment and enrollment. We work relentlessly to diminish the time lag from idea to implementation. We have already developed efficiencies within our system that may be applicable elsewhere. Our CTSC is well positioned to profit from our own and others' improvements in clinical trial management.

AIM 5: INFORMATICS

Bioinformatics: Our Informatics teams develops creative solutions to the challenges facing C/T research today. They apply novel approaches to our core laboratory facilities, "big data," clinical information, and drug discovery. All of these are essential to our collaborative approach to respond to unmet health needs with efficiency, quality, and economy, and to promote methodologies that are increasingly personalized and effective for appropriately selected populations. For example, in the **bioinformatics** space, our proteomics core produced novel analytics for both proteomic and genomic analysis. Education in this space is also promoted: proteomics was the home base of a new graduate program in Systems Biology and Bioinformatics, begun in 2011, which has been popular in the CTSTP (TL1). Genomics facilities have grown to provide both sequencing and analytics, with more extensive analytics in ICB bioinformatics. These cores received support from the CTSC for access and consultation and our pilot program supports investigators in determining utility of the various techniques for their own projects.

As clinical studies more and more require large participant pools from multiple sites, data collected at disparate locations with differing instrumentation are often difficult to reconcile. GQ Zhang, PhD in our Department of Electrical Engineering and Computer Sciences, working at the **interface between bioinformatics and clinical informatics,** developed informatics systems to harmonize data collected in different electronic systems for sleep

or epilepsy studies.[76] Though Dr. Zhang has left CWRU, this work is continued by Satya Sahoo, PhD.[77-79] We have made these programs available throughout the consortium on request.

Inventive use of **informatics and big data** by Rong Xu, PhD, developed novel computational drug discovery approaches that translate observed phenotypic perturbations caused by drugs or diseases in humans into novel disease treatments.[80-82] She used this drug repositioning strategy to identify new leads to treat schizophrenia, dengue fever, and Parkinson disease. Now she is using computational approaches to identify candidates among FDA-approved drugs to treat ovarian cancer. She will clinically corroborate top-ranked drug candidates using patient electronic health records, and test top-ranked drug candidates in cell lines derived from ovarian cancer patients. She will apply novel computational approaches and big data to decipher the interplay between host genetics, microbiome, and colorectal carcinogenesis. For example, TMAO, a gut metabolite produced by bacteria, is strongly correlated with colon cancer development.[83] Dr. Xu joins the *Informatics* component of the CTSC to consult with investigators about development of new methodologies.

Medical informatics: Clinical/medical informatics has evolved at different rates across our affiliated hospitals, partly because the EHR vendors are different and deployment is at different stages. CC and MH are longtime users of Epic (though different versions), and UH recently deployed AllScripts, but different programs for inpatient and outpatient use. New tools have been developed to assist in **mining the electronic health record (EHR)** for pertinent data. For example, eResearch, an EHR add-on developed at CC, evolved into Explorys, Inc., a spinout company from CC acquired by Watson Health/IBM. eResearch is used within CC to identify subjects for clinical studies and sweep clinical studies data into a research database (for examples, see above); Explorys has access to over 50 million separate records and can link the records of patients seen at multiple locations, or allow mining of that large, de-identified database. All our hospitals except VA have purchased Explorys. Thus, at the moment, we have the capability not only to focus within a system (using eResearch at CC and Explorys at the other locations), but also to access a larger de-identified patient pool (for publication, permission must be sought from the institutional contributors). This technology offers the opportunity to collate observations across multiple EHRs, identify and select patient populations suitable for clinical trial, identify associations of phenotypes with particular drugs or conditions, and more. For example, eResearch also has been used to generate the data sets used by Michael Kattan, PhD and his group to generate prediction equations for either risk or outcomes for certain common diseases. These predictors assist in clinical decision making and also in informing patients of their therapeutic choices (e.g., [84-86]). As our approaches evolve this year, i2b2/SHRINE, CLEARPATH and the SHED, and TriNetX will add to the available tools for EHR search and expand other capabilities.

Our informatics leaders at MH are nationally recognized in medical/clinical informatics. The Health Information Management and Systems Society (HIMSS) recognized MH with the **2015 Davies award for its use of health IT to improve patient outcomes**. MH mines its EHR (Epic) with Explorys to identify subjects and conduct preliminary and confirmatory studies.[87] David Kaelber, MD, the CMIO at MH and co-lead of CTSC informatics, is Board certified in Clinical Informatics and obtained accreditation for a fellowship in this specialty in coordination with the Department of Population and Quantitative Health Sciences (Dr. Haines, Chair), which houses the didactic portion of the fellowship and offers a new MS in Clinical Informatics. MH has led in demonstrations of EHR utility. The Better Health Partnership (BHP), based at MH, showed that improvements in process and outcome in patients with chronic diseases were better in practices that had the EHR than in those that did not.[57].

De-identified EHR data (plus laboratory information) from CC, MH, and UH will come together in the SHED (Securely Held Electronic Data) for data collected in studies and CLEARPATH, a secure data repository developed by Jonathan Haines, PhD, which will serve as a medical informatics resource for the entire academic biomedical enterprise in Cleveland. This resource is explained in the subsequent *Informatics* component. EHR data from one of our hospital partners (UH) is in the process of generating a hashed-ID in preparation for migration to CLEARPATH. Of course, after a small sample has migrated, we must verify all of the security and integrity parameters, but once that is complete, migration of data should accelerate. In order to assure sharing of deidentified data we are installing i2b2 and SHRINE (used at many CTSAs), and also have engaged with TriNetX (at 24 other CTSAs) to facilitate sharing deidentified data among CTSA Hubs. Important advantages of CLEARPATH beyond simply a shareable deidentified data set are that it can also manage genomics, proteomic and gene expression data, as well as information from mobile devices and other important correlates of the clinical condition. In addition, there is also opportunity to correlate health information in CLEARPATH with demographic, environmental, crime, and socioeconomic data contained in the “NEO CANDO” data base maintained at the Mandel School of Applied Social Sciences (e. g., [88]), and with the population health information contained in the Health Data Matters database maintained by the Urban Health Initiative. Given the importance of social and environmental influences on health, this capability has great potential. Another

substantial advantage is that once data from all three participating health systems is migrated, we expect to have upwards of 80% of the population in the seven-county area around Cleveland, rich in ethnic and economic diversity, in the data set, an extraordinary opportunity for population based studies. Expanded capability for correlative studies distinguishes CLEARPATH from most common, combined data sets now in use. Another collaborative tool that is fully operational is SHED, a secure data repository that contains the results of more than 1000 clinical studies, whose PIs have agreed can be used, de-identified, to validate or test new hypotheses. SHED contains only research quality data from tens of thousands of participants and allows quick looks at hypotheses that otherwise might take years to investigate.

Collection, processing, and application of **data from mobile devices** is being piloted in many disciplines. For example, a project at CC is studying the value of mobile device monitors in patients with heart failure. More extensive pilot programs in the obesity space utilize a sensor armband that measures metabolic rate minute by minute (Metaboloss, developed at CWRU) and are testing whether, in patients enrolled in a Weight Watchers at Work program through MH, there are "resets" of the metabolic rate when weight loss occurs. Metabolic markers are correlated with nutritional and other weight loss markers, and are being correlated with movement detected with wearable sensors, to inform treatment in Parkinson's disease, depression, wasting in HIV or cancer.

Health IT offers enormous potential to improve health and to individualize treatment plans for common disorders such as obesity, hypertension, heart failure, and others. However, contributing to health disparities is the "digital divide": at MH, our public safety net hospital, only 25% of their patients access the electronic portal that contains their health data and provides access to the system. One barrier to acting upon these pilot findings is the fact that in Cleveland, internet capacity and devices are often unavailable or inaccessible to poor neighborhoods or those without technical facility (the poor, the elderly, the less educated). The populations that lack connectivity often contain an excess of members with chronic diseases that may be helped by such mobile monitoring. New local and federal initiatives to offer broadband to low income populations therefore afford a great opportunity to improve health. The Federal Communications Commission recently recognized our effort among the Urban Health Initiative, the MetroHealth Patient Centered Media Lab, and other community organizations to increase technologic access and literacy among vulnerable populations. This successful collaboration will enable the CTSC's efforts on **digital health** to address the needs of all of our populations.

We intend to work toward interoperable solutions to Big Data and informatics issues. To this end, not only will we share technologies that we develop in our CTSC (as we have previously for the programs of GQ Zhang and S Sahoo such as Physio-MIMI, MiDas, and others) [89,90], but we already have adopted REDCap, ResearchMatch, i2b2, SHRINE, and a VIVO-based program for tracking investigators to promote collaborations. We are eager to learn from others and adopt best practices, and to contribute some of our own.

SUMMARY AND CONCLUSIONS

Our CTSC aims to improve the health of our nation by providing superbly trained C/T researchers who will bring discoveries from our laboratories to the patients and will disseminate knowledge to improve the health of our communities. Over the last decade, the CTSC has developed a strong collaborative culture, both among its members and with external entities such as biotech companies, public health departments, and community agencies. These collaborations enabled us to move the needle in health statistics in Cleveland, and create the opportunity for the CTSC to catalyze further improvements. We are now tackling the especially vulnerable population of children—both in translating our laboratory discoveries to benefit children, and in applying what we know to improve infant mortality, childhood obesity and inactivity, and childhood asthma. Our collaborations also allow us to move our discoveries expeditiously from the laboratory to patient testing, then through the FDA process to benefit patients. By combining this expertise with our genomics and informatics strength, we will enhance the delivery of personalized medicine. Our strength in informatics and health IT will be applied not only for new discovery research and hypothesis generation, but also to improve patient care with remote monitoring, easy health information flow, and continuous quality improvement based on analytics of the clinical data.

This strong research position provides a great training opportunity for learners at the undergraduate, graduate, professional student, postdoctoral/fellow, and junior faculty level. The research environment, combined with our dedicated, innovative and effective educational policies, provides fertile ground in which learners can grow and flourish. We develop careers in C/T research not only at the learner level, but also at the faculty level by providing appropriate rewards for team science, by creating core facilities and infrastructure to support C/T research, by responding to new opportunities rapidly and with flexibility, and by recognizing and supporting the critical role of C/T research in the health of our nation.

A. Administrative Core

SPECIFIC AIMS

Since its inception, the Clinical and Translational Science Collaborative (CTSC) of Cleveland has transformed its research community. Today it operates as a fully integrated cooperative, collaborative, and confluent research environment that supports all aspects of clinical and translational science, enabling full access by university faculty at all partner institutions to all CTSC-associated potential collaborators and research resources. It has positioned itself to assume leadership in disseminating best practices and promoting multi-site clinical research. It now seeks funding to support the development of program support required to advance the goals set forth by the 2013 recommendations for the CTSA Program by the IOM (now NAM).

The CTSC is a collaborative among Case Western Reserve University (CWRU) SOM and its four affiliated hospital systems. Three as primary partners, the Cleveland Clinic (CC), MetroHealth (MH), and University Hospitals (UH). The Louis Stokes Veterans Administration Medical Center (VA) as a limited partner. Other CWRU schools that participate in the CTSC include the schools of Nursing, Engineering, Dental, Management, Applied Social Sciences, Law, and Arts & Sciences. CTSC partners are described in greater detail under "Approach". All but MH are located in the University Circle area of Cleveland and within walking distance of each other; MH is eight miles to the west. The CTSC, along with community partners, have forged a powerful and effective Hub for clinical and translational research and training over the past decade. We work remarkably well together, in a collaborative, cooperative, and collegial manner to advance the goals of the CTSC.

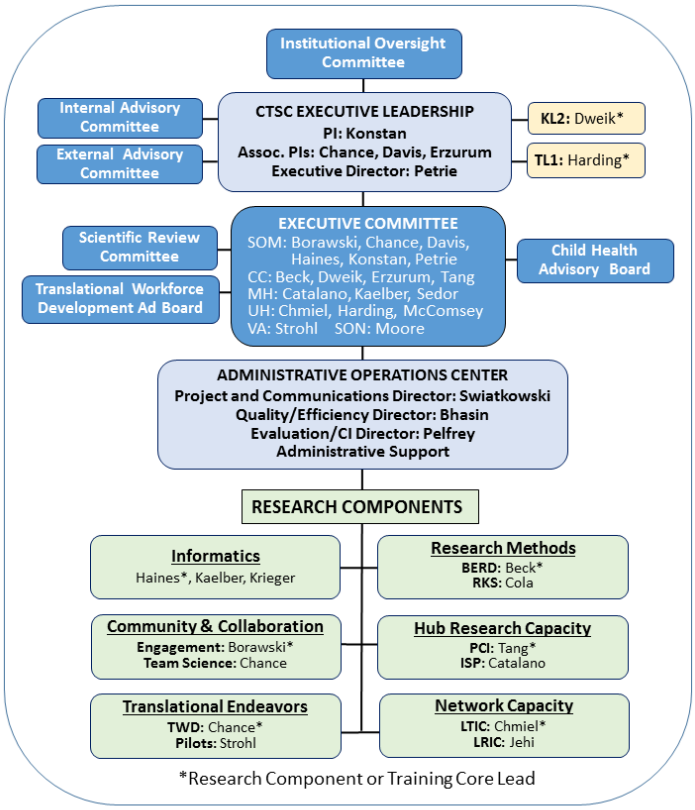


Figure 1. CTSC Organizational Structure

The goals of the CTSC are aligned with the goals of NCATS CTSA program (described in Overview). The organizational structure of the CTSC, as shown in Figure 1, reflects this alignment. We have established an *Administrative Core* which includes leadership, governance and operational management for the program. Oversight and advice to the PIs and administrative leadership is provided by seven committees/advisory boards (in blue). There are six clinical/translational (C/T) research components: *Informatics, Community and Collaboration, Translational Endeavors, Research Methods, Hub Research Capacity, and Network Capacity (in green)*; and two formal C/T training cores: *Institutional Career Development Core (KL2),* and the *NRSA Training Core (TL1) (in yellow).*

The **Administrative Core** will support and advance the goals of the CTSC of Cleveland through the following **specific aims**:

Aim 1: Provide effective **leadership** and **governance** within an interactive **organizational structure** to support the ongoing growth and innovative opportunities of the research and research training enterprise.

Aim 2: Ensure the integration of clinical research services and training among the CTSC partner institutions (Hub) and the national CTSA network that will assure opportunities for multi and trans-disciplinary **collaboration** and **communication.**

Aim 3: Provide comprehensive **evaluation** and tracking of CTSC metrics, milestones and measurable performance within the framework of the national CTSA evaluation program to foster **continuous improvement**.

Aim 4: Ensure high **quality** and **efficiency** in the conduct of safe human research among the CTSC partner institutions, and to share best practices within the Hub and with the national CTSA network.

APPROACH

Aim 1: Organizational Structure, Governance, and Leadership

The organizational structure, governance and leadership of the CTSC of Cleveland supports and encourages dynamic interactions between the partner institutions, fully integrates the partnership members, and enables access to all who wish to participate. The organizational structure has produced a surge of new research within the partner institutions and the Cleveland community. Figure 1 shows the organizational structure of the CTSC, and the integration of the six research components and two training cores. Internal and external committees support and/or advise the PIs, Executive Committee, research components, and training cores.

CTSC Executive Leadership is vested in the Principal Investigator, Michael W. Konstan, MD, and three Associate Principal Investigators, Pamela B. Davis, MD, PhD, Mark Chance, PhD, and Serpil Erzurum, MD. The PIs have primary responsibility for leading the CTSC and for ensuring the success of its structure. They have reviewed the 2013 IOM report, discussed strengths which the CTSC might exploit to respond to the IOM (now NAM) recommendations, and are prepared to work diligently to develop the next iteration of the CTSC, in keeping with the emerging needs of C/T research. The Executive Director, Ginny Petrie, guides the leadership in mapping out strategic plans, ensuring coordination between sites, obtaining data on financial and budgetary management, and overseeing overall day-to-day operations of the program. The Executive Leadership group meets weekly (Table 1) to assure that all aspects of the CTSC are operating smoothly and efficiently, and to quickly identify and manage any problematic issues or concerns.

The **Executive Committee** is the primary governing body of the CTSC, and is composed of the Executive Leadership and the leads of the six clinical and translational research components [*Informatics, Community and Collaboration, Translational Endeavors, Research Methods, Hub Research Capacity, and Network Capacity*] and the two formal C/T Training Cores [*Institutional Career Development Core (KL2) and the NRSA Training Core (TL1)*]. Select co-leads serve on this committee to assure proportionate representation from CTSC partners. The Executive Committee meets monthly to address issues pertaining to coordination across programs, individual program effectiveness, efficient and effective resource utilization, and reallocation of resources as appropriate to meet program needs.

In addition to the Executive Committee, there are five internal committees/advisory boards and one external committee. An **Institutional Oversight Committee,** constituted by the CEOs or Presidents of the primary participating institutions (CWRU-Barbara Snyder; Cleveland Cleveland-Delos Cosgrove, MD; MetroHealth-Akram Boutros, MD; University Hospitals-Daniel Simon, MD) will provide input to issues that require policy changes or overarching institutional issues. An **Internal Advisory Committee (IAC)** is composed of the CWRU deans of the schools of Nursing, Dental Medicine, Engineering, and the executive dean of the Cleveland Clinic Lerner College of Medicine; critical center directors from the SOM (including the Case Comprehensive Cancer Center and the Center for Child Health and Policy), representatives from each of the three primary hospital partners and the VA, civic and community members (including the commissioner of the Cuyahoga County Board of Health), and patients who participate in clinical trials. This group meets biannually and as needed to provide advice to the CTSC executive leadership. Topics addressed include progress of CTSC components, internal and external partnership issues, and evaluations from the directors of Evaluation and Continuous Improvement, and Quality and Efficiency. **Scientific Review Committee (SRC)**, **Translational Workforce Development (TWD) Advisory Board,** and **Child Health Advisory Board** consist of members from participating institutions. The SRC meets monthly, the TWD Advisory Board meets biannually. Detailed information regarding the composition and role of the SRC Committee and TWD Advisory Board are presented elsewhere in this application (see *Translational Endeavors* and the two training cores). The Child Health Advisory Board, which also includes members from the community and patient consumer representation, meets biannually and as needed to provide advice to the CTSC leadership regarding issues related to child health. An **External Advisory Committee (EAC)** assembles annually to provide external input and advice into various aspects of our program, bring external perspective to the table, and spark collaborations across institutions (see Table 2 for membership). The EAC, which most recently convened in February 2017, provides a list of specific issues and related recommendations to which the CTSC must provide specific responses and/or implement improvements in its program (see Specific Aim 3).

Table 1: Committee Meeting Schedule

Executive Leadership	Weekly
Executive Committee (EC)	Monthly
Scientific Review Committee (SRC)	Monthly
Translational Workforce Development (TWD) Ad Board	Biannually
Child Health Advisory Board	Biannually
Internal Advisory Committee (IAC)	Biannually
External Advisory Committee (EAC)	Annually

The **Administrative Operations Center,** overseen by the Executive Director, provides overall support to the CTSC, and houses a project and communications director, and the administrative directors who oversee our commitment to Evaluation and Continuous Improvement, and Quality and Efficiency (described under specific aims 3 and 4 below). Other administrative personnel assist with the day-to-day operations of the CTSC. The CTSC is supported by the Office of Research Administration at the SOM.

Leadership (See Biosketches for personal statements and academic/professional achievements)

1. Executive and Administrative Leadership:

Michael W. Konstan, MD, Principal Investigator, is Vice Dean for Translational Research at the School of Medicine. As PI, Dr. Konstan will be responsible for the overall design, implementation and operation of all functions of the CTSC, and for facilitation of child health initiatives of the CTSC. Dr. Konstan, professor of pediatrics at CWRU, assumed direction of the CTSC in 2015 with his Vice Dean appointment. His appointment as PI of the CTSC was a natural fit, based on his broad experience creating clinical and translational consortia and networks for advancing research in cystic fibrosis and for helping to found the Cystic Fibrosis Foundation Therapeutics Development Network, in addition to directing a P30 Clinical Studies Core and leading a K12 program in Child Health. The cystic fibrosis story is a compelling example of facile movement from basic discoveries through clinical trials, to possible cures, and Dr. Konstan has been in the midst of this exemplary journey in major leadership roles. He has led many national and international trials of CF drugs that have made their way to patients, including drugs targeting the underlying defect of CF. His work extends beyond cystic fibrosis; he is currently leading Cleveland's effort to reduce infant mortality through a collaborative that involves CWRU, Cleveland's healthcare institutions, Cleveland City and Cuyahoga County government agencies, and many community organizations. He was recently selected by the Ohio Department of Medicaid to lead the state-wide Cardiovascular Disease (CVD) Collaborative to improve the control of hypertension in Ohio; a collaborative that includes two other universities that house CTSA Hubs (Ohio State University and University of Cincinnati).

Pamela B. Davis, MD, PhD, Associate Principal Investigator, is Dean of the School of Medicine and Senior Vice President for Medical Affairs at Case Western Reserve University. As Associate-PI, Dr. Davis will be responsible for facilitating collaborations outside of Cleveland, with the community and industry. As dean of the School of Medicine, she holds a unique position of academic leadership over CWRU faculty at all affiliated institutions (CC, MH, UH, VA) and is a strong institutional CTSC supporter. Dr. Davis was PI of the CTSC from its inception in 2007 until 2015, and built a remarkable collaborative research and training environment spanning the city of Cleveland and beyond, as described in the Overall section. She has positioned the CTSC well to contribute to the goals of the new iteration of the CTSA program. Dr. Davis, a member of the National Academy of Medicine, has a distinguished basic and translational research career in cystic fibrosis, having been continuously funded by the NIH since arriving at CWRU in 1981. Dr. Davis has trained many notable physicians and scientists throughout her career. She was among the first physicians to devote their clinical care to adults with CF, and is a champion of bench-to-bedside and back again. Dr. Davis has served on NCATS Council, as well as several External Advisory Boards for CTSA Hubs.

Mark Chance, PhD, Associate Principal Investigator, is the Vice Dean for Research and Graduate Education at the School of Medicine. As Associate-PI, Dr. Chance will oversee activities in the *Community and Collaboration* and *Translational Endeavors* components of the CTSC. Within these components, he will lead Translational Endeavors (directing Workforce Development), and will be an integral part of Community and Collaboration, particularly with regards to Team Science. Dr. Chance also chairs the TWD Advisory Board, which interfaces with the six C/T research components and two C/T training cores. Dr. Chance is an international expert in proteomics, systems, and structural biology. His laboratory invented mass spectrometry-based protein footprinting, widely used to examine protein structure. Since coming to CWRU to establish the Center for Proteomics and Bioinformatics in 2005, Dr. Chance has developed core resource and technologies to provide advanced systems biology assessment of disease, resulting in novel biomarkers and disease classifiers. Dr. Chance heads the commercialization program that is intended to accelerate the development of laboratory discoveries into therapeutics, which is anchored at the School of Medicine but available to faculty across the CTSC. Dr. Chance is also co-PI of the National Center for Advancing Innovations (NCAI, funded by NHLBI), and is the resource for identifying all city-wide technologies and innovations for the CTSC.

Serpil Erzurum, MD, Associate Principal Investigator, is Chair of the Lerner Research Institute at Cleveland Clinic and a pulmonary and critical care physician. As Associate-PI, Dr. Erzurum will oversee the activities of the *Research Methods, Hub Research Capacity*, and *Network Capacity* components of the CTSC, as well as the Quality and Efficiency program. Her groundbreaking contributions and leadership in C/T pulmonary research

have led to diagnostic and therapeutic advances in lung diseases. Her landmark discoveries formed the framework for noninvasive measure of nitric oxide (NO) in exhaled breath, now a widely applied pulmonary function test for monitoring airway inflammation and asthma control. Dr. Erzurum currently leads two program project grants, provides leadership to two NHLBI networks, and serves on the Advisory Council for NHLBI. Her work has been highly collaborative across the city, and nation.

PI or Associate-PI Leadership Succession Plan: If Dr. Konstan becomes unable to serve, Dr. Davis will assume the interim role until she and the President of CWRU nominates either a permanent replacement or an interim leader (pending a national search). If Dr. Erzurum becomes unable to serve, the CEO of the Cleveland Clinic, in consultation with the PI, will nominate a replacement, either permanent or interim. If Dr. Davis or Dr. Chance becomes unable to serve, the President of CWRU together with the PI will nominate a replacement, either permanent or interim. Any replacement will be named only after consultation with the Institutional Oversight Committee (which consists of the most senior executive leader of CWRU, CC, MH and UH).

The **Executive Director, Ginny Petrie**, is a crucial partner with the PI, Associate-PIs, and senior leadership team of the CTSC, making recommendations on fiscal, personnel, programmatic and strategic development issues and initiatives of the CTSC to assure that all activities are aligned with its mission. She will be responsible for the day-to-day administrative operations of the CTSC, and has done so since the inception of the CTSC. She works with internal and external partners and contacts in an effort to engage communities, stakeholders, and scientists in furthering translational research. Ms. Petrie has a 30+ year track record of executive and administrative management at CWRU/UH, 26 of them working with Drs. Konstan and Davis. She is administratively savvy and thoroughly integrated into the upper management of the CTSC and leadership of the School of Medicine. She is assisted by administrative managers, assistant directors, and a financial analyst, and works closely with the relevant offices at CWRU and partner institutions to be sure that management, grant operations and resource deployment occur smoothly. She meets weekly with Dr. Konstan and the Associate-PIs, and has direct and immediate access to Dr. Konstan. Ms. Petrie will also oversee the activities of the Administrative Operations Center, and the **Research Concierge, Carolyn Apperson, MS,** who is the front door to linking young and other investigators to access the services of the CTSC.

2. Clinical and Translational Research Component and Training Core Leadership: (See Biosketches for personal statements and additional academic/professional achievements, and individual components presented elsewhere in this application for lead roles in the CTSC).

Informatics will be co-led by **Jonathan Haines, PhD** (Designated Component Lead), Director of the Institute for Computational Biology, Chair of the Department of Population & Quantitative Health Sciences at CWRU SOM, and director of our current CTSC's Bioinformatics Core, **David Kaelber, MD, PhD,** Chief Medical Informatics Officer for MH and the lead of medical informatics for the CTSC; and **Mitchel Krieger, MD**, Associate Chief Information Officer for CC. **Jeffrey Sunshine, PhD, MD,** Chief Medical Information Officer for UH will provide support to Dr. Haines for UH's EHR. Drs. Kaelber, Krieger, and Sunshine are responsible for their respective hospital system's EHR and other informatics tools for use by the CTSC.

Community and Collaboration will be led by **Elaine Borawski, PhD,** director of the CDC-funded CWRU Prevention Research Center for Healthy Neighborhoods, and co-director of our current CTSC's Community Partnership Core. Dr. Borawski will lead the overall component, but will share leadership with **Kurt Stange, MD, PhD**, co-director of our current CTSC's Practice Based Research Network (PBRN) Core, and a member of the National Academy of Medicine and **Mark Chance, PhD** (described above). As described in the C&C section, the composition of this team is intentional - each of these individuals has a highly successful track record of leading teams in collaborative, translational endeavors within their own areas of expertise: basic science and team science (Chance), clinical/PBRNs (Stange) and community/public health (Borawski). **Shirley Moore, PhD, RN**, Associate Dean for Research for the School of Nursing, will provide support to the leadership team in the development and implementation of our team science training activities.

Translational Endeavors will be led by **Mark Chance, PhD** (described above). Dr. Chance will lead the *Translational Workforce Development* sub-component with co-lead **Ofer Reizes, PhD,** director of Skills Development NSF I-Corps at CC. **Kingman Strohl, MD,** director of the CWRU Center for Sleep Disorders Research at UH and VA, will lead *Pilot Translational and Clinical Studies*, with co-leads **John Sedor, MD**, Vice President for Research at MH, and **John Kirwan, PhD**, director of the Metabolic Translational Research Center at CC. Dr. Strohl chairs the Scientific Review Committee for the CTSC, and is transforming the committee to cope with new challenges of multi-site studies, reliance IRBs, and participation with coordinating centers to gain rapid approval of trials. Dr. Strohl is a member of NCATS's recently developed CTSA VA working group.

Research Methods will be led by **Gerry Beck, PhD,** Section Head of Clinical Trials Design and Analysis in the Department of Quantitative Health Sciences at CC. Dr. Beck will continue to lead *Biostatistics, Epidemiology, and Research Design (BERD)*, with co-leads **Douglas Einstadter, MD** (MH) and **Sara Debanne, PhD** (SOM). **Philip Cola, PhD**, former VP of the UH Clinical Research Center and now at the Weatherhead School of Management at CWRU, will continue to lead *Regulatory Knowledge and Support (RKS)*, including the IND/IDE Core. Dr. Cola has been active in CTSA activities on a national level, displaying leadership and resourcefulness in participating with other CTSA Hubs. He currently leads our CTSC's participation in the Scientific Review Committee pilot project led by the Tufts CTSA, and remains active in a leadership role in the ongoing reliant IRB initiative led by the Dartmouth CTSA. Dr. Cola will be assisted by co-lead **Carey Gorden, JD (MH)**. **Kathy Lawry, MSSA**, retired from MH, is our SMART IRB Ambassador.

Hub Research Capacity will be led by **W.H. Wilson Tang, MD**, director of the Clinical Research Unit at CC. Dr. Tang will lead *Participant and Clinical Interactions (PCI)*. **Patrick Catalano MD,** director of the Clinical Research Unit at MH, will lead *Integrating Special Populations (ISP).* Drs. Tang and Catalano will be assisted by **Grace McComsey, MD,** Associate Chief Scientific Officer and director of the Clinical Research Unit at UH. These three leaders meet regularly and have established a collaborative team to conduct C/T research for the CTSC.

Network Capacity will be led by **James Chmiel, MD, MPH,** former director of the CF Therapeutics Development Center at CWRU and UH, and by **Lara Jehi, MD**, associate director of the Clinical Research Unit and research director of the Epilepsy Center at CC. Dr. Chmiel will lead our Trial Innovation Unit (TIU) and serve as *the Liaison to Trial Innovation Centers (LTICs),* and Dr. Jehi will lead our Recruitment Innovation Unit (RIU) and serve as *the Liaison to the Recruitment Innovation Center (LRIC)*. Drs. Chmiel and Jehi serve as Co-Medical Directors of our Trial Innovation Network (TIN) Hub Liaison Team.

Institutional Career Development Core (KL2) will be led by **Raed Dweik, MD.** Dr. Dweik is the current director of our CTSC-supported Mentored Career Development (*KL2*) Program. He is the director of the Pulmonary Vascular Program, Department of Pulmonary, Allergy, and Critical Care Medicine at CC. He will be assisted by associate directors **Clifford Harding, MD, PhD** (*TL1* director) CWRU SOM /UH; **Shirley Moore, PhD, RN**, CWRU School of Nursing, and **James Spilsbury, PhD**, CWRU SOM.

NRSA Training Core (TL1) will be led by **Clifford Harding, MD, PhD.** Dr. Harding is the current director of the Clinical and Translational Scientist Training Program (CTSTP) of our CTSC (TL1 supported). He is the Chair of the Department of Pathology at CWRU and UH, and directs the Medical Scientist Training Program (MSTP) at the SOM, and the CTSTP since its inception. He will be assisted by associate directors **Raed Dweik, MD (***KL2* director) CC; **Shirley Moore, PhD, RN,** CWRU School of Nursing; and **James Spilsbury, PhD**, CWRU SOM.

3*. Membership of the External Advisory Committee:*

Table 2: External Advisory Committee*

Name / Affiliation	Positions	Area of Expertise
Jennifer DeVoe, MD, DPhil Oregon Health Science University	Exec Director, OCHIN Practice-Based Research Network; Associate Professor of Family Medicine	Community practice and policy interventions in vulnerable populations
Patrick A. Flume, MD Medical University of South Carolina	Associate PI, CTSA; Assistant Provost of Research Compliance and Regulatory Affairs; Professor of Medicine and Pediatrics	Research compliance and regulatory affairs; clinical research; pulmonary/critical care
James Heubi, MD University of Cincinnati	PI, CTSA; Associate Dean, Clinical and Translational Research; Professor of Pediatrics	Clinical and translational research; pediatrics; gastroenterology
Julianne Imperato-McGinley, MD Weill Cornell Medical College	PI, CTSA; Associate Dean, Translational Research & Education; Professor & Chief of Endocrinology	Clinical and translational research; endocrinology; med student training
Philip Payne, PhD, FACMI The Ohio State University	Associate Director for Data Sciences, CTSA; Professor and Chair of Biomedical Informatics	Clinical research informatics; translational bioinformatics
Geoffrey Thrope NDI Medical	Chief Executive Officer and Managing Director	Commercialization and device development
Victoria Tifft, MBA Clinical Research Management, Inc.	Chief Executive Officer	Compliance and regulatory affairs; commercialization
Katherine White National Cystic Fibrosis Foundation	Adult with cystic fibrosis; Member, Board of Trustees; Chair, Adult Advisory Council	Clinical trial subject participation; Chronic disease management
John Yates III, PhD The Scripps Research Institute	Professor, Chemical Physiology and Molecular and Cellular Neurobiology	Bioinformatics; biomarkers
Yun Yen, MD, PhD Taipei Medical University	President; Professor, Institute for Cancer Biology and Drug Discovery	Cancer biology and drug discovery
Andrew Young, MD, PhD Quest Diagnostics	Medical Director	Academic-industry partnerships; gene profiling and data informatics

*we have not solicited new members who will come on in rotation in the next grant period, to keep the Committee fresh.

Partner Institutions and Their Contributions to the CTSC of Cleveland

The CTSC is the product of a collaboration between CWRU School of Medicine (SOM) and other CWRU schools, and the major hospital systems in the city of Cleveland. The SOM lies at the heart of the collaborative, and serves as the hub for the hospital partners, all of whom have affiliation agreements with CWRU. Cleveland Clinic (CC), MetroHealth System (MH), and University Hospitals Health System (UH) serve as primary partners in the collaborative, and The Louis Stokes Veterans Administration Medical Center (VA) which shares many faculty with MH and UH serves as a limited partner. 2,560 physicians and scientists at the affiliated hospitals have full-time faculty appointments at the SOM; each of the hospital systems have robust C/T research programs that interface with the SOM; each of the partners trains medical students, residents, and subspecialty fellows; and each participate in city-wide clinical and research collaborations (e.g. the Case Comprehensive Cancer Center).

Although the CWRU and each of the hospital systems are under separate management, the CTSC has achieved a high degree of collaboration at the level of faculty and investigators with the result that all of our committees and many of our projects have participants from all of the partner institutions. Each hospital partner serves somewhat different populations, providing a diverse population of patients available for research participation. CC is a large, highly-ranked group practice and subspecialty care referral hospital, MH is the public safety net hospital for Cuyahoga County, UH has a large academic medical center with a nationally prominent children's hospital, and the VA serves our nation's veterans, many of them elderly. Together, these hospital systems provide care for 90% of the eight-county Cleveland area, and subsume a diverse population across the lifespan (Table 3). More than three million lives are covered in EHRs at the three primary hospital partners. All three and the VA are actively engaged in NIH or other federally funded clinical trials. Our capacity to enroll in multi-site clinical trials is enormous given the population we serve, as is our capacity to aggregate their health information into a harmonized database (except for the VA). (See *Informatics*). What bonds us together and enables the collaborative to work is that the SOM is the academic home for all four health systems, and we share a common mission, to better the health of our community, to bring our discoveries to patients, and to train the next generation of physicians and scientists. We are committed to making the institutions more accessible to the community and the professionals who emerge from the institutions better prepared to serve their communities both as investigators and as deliverers of higher standards of care.

Table 3: Clinical Partner Institutions*

	Cleveland Clinic	University Hospitals	Metro Health	VA
2016 Lives Covered (EHR)	2.2 M*	1.2 M	0.6 M	
Annual Outpatient Visits	7.1 M*	2.5 M	1.05 M	2.0 M*
Annual Patient Admissions	222,059*	144,728	27,621	11,826
Community hospitals	8	11	0	0
Current NIH/Fed Clinical Trials per ClinicalTrials.gov (5/2017)	1060	905	102	N/A
Full-time Faculty CWRU SOM	1002 (CCLCM)	936	499	123

*Data from most recent Annual Reports

Specific contributions of partner institutions to the CTSC:

CWRU School of Medicine (SOM): The CWRU SOM is the leading medical research and training institution in Ohio, ranking 25th among 140 U.S. medical schools in research (USNWR, 2017) and 17th in NIH funding (SOM and CCLCM-CWRU combined). The full-time faculty of the SOM number 2,824 and consist of basic and clinical/translational researchers and physicians based at the SOM and our affiliated hospital systems. CWRU SOM is the home for many NIH, CDC, and foundation supported research centers, including the Case Comprehensive Cancer Center, Center for AIDS Research, Prevention Research Center for Healthy Neighborhoods, Cleveland Digestive Diseases Research Core Center, GI Cancer SPORE, BETRnet for upper GI cancer, Visual Sciences Research Center, Skin Diseases Research Center, National Center for Regenerative Medicine, and the Cystic Fibrosis Therapeutics Development Center, among others. National leadership in clinical trials is documented in the overall section. Although the programmatic and administrative functions of these Centers are based at the SOM, subject participation occurs within the clinical research facilities at CC, MH, UH, and the VA, including their expansive community sites throughout northeast Ohio. Many technology and support cores at the SOM provide services to our basic, translational, and clinical research programs throughout the city. The Institute for Computational Biology (ICB), jointly supported by CWRU, CC and UH, is housed at the SOM, and is directed by CTSC *Informatics* lead, Dr. Haines. The ICB designed and manages the centralized databases used to support C/T research for the CTSC. In addition to Dr. Haines, other CTSC leadership based at the SOM include Drs. Borawski and Stange (*Community and Collaboration*), Dr. Chance (*Translational Endeavors* lead and Associate-PI), and Drs. Konstan (PI) and Davis (Associate-PI). CWRU SOM training programs for MD students include a large

MSTP and CTSTP program, 160 students at CCLCM who spend an additional year in research, and many students who obtain the MS or MPH in addition to the MD degree (anatomy, bioethics, clinical research are most popular), over 1000 grad students (MS and PhD), as well as longstanding pipeline programs for undergraduates from underrepresented minority groups. The SOM stands among the top 10% of US medical schools in graduating African American physicians, and among the top 15% for contributing medical school faculty.

Cleveland Clinic (CC): Cleveland Clinic consistently ranks as one of the nation's five best hospitals in USNWR annual America's Best Hospitals survey. The heart program has ranked number one in America for 22 consecutive years. CC also ranks among the nation's top ten in 13 of 16 subspecialties. Patients come from all 50 states and 147 countries to receive care at CC. In addition to its main campus (contiguous with the campus of CWRU), CC has a network of community hospitals and outpatient centers in Northeast Ohio, and maintains sites in Florida, Nevada, Toronto, London, and Abu Dhabi. Cleveland Clinic is a pioneer in internet-based medicine and internet-based research tools. CC leads the nation in information technology for research, many of which benefit our CTSC, including eResearch, Knowledge Program (KP) and Explorys, the latter licensed to IBM/Watson for advances in healthcare technology. CC offers clinical services through eClevelandClinic. The Lerner Research Institute (LRI) coordinates and oversees laboratory-based C/T research at CC. More than 1,200 scientists and support personnel work directly within the LRI's 700,000 sq. ft. of lab and C/T research space. In addition to research within the LRI, CC's Clinical Institutes conduct translational and clinical research, including the Cole Eye Institute, the Heart and Vascular Institute, the Neurologic Institute and the Taussig Cancer Institute (associated with the SOM's NCI designated Case Comprehensive Cancer Center). CC also is one of three NIH Centers for Accelerated Innovations, and partners with CWRU, Ohio State University, University of Cincinnati, and Cincinnati Children's to accelerate the translation of NHLBI-supported discoveries and technologies into new products. The strong commitment of CC to education, particularly C/T research education, is manifest not only in its fellowship program and many applicants for KL2 scholars, but also by the track in the SOM that CC supports, the CC Lerner College of Medicine of CWRU – a five-year program dedicated to training the next generation of physician-investigators. In addition to Associate-PI Dr. Erzurum, who provides oversight for *Research Methods*, *Hub Research Capacity*, and *Network Capacity*, leadership of *Informatics* (Dr. Krieger), *Translational Endeavors* (Dr. Kirwin), *Research Methods* (Dr. Beck), *Hub Research Capacity* (Dr. Tang), *Network Capacity* (Dr. Jehi, LRIC), and the *KL2* (Dr. Dweik) are based at CC. Dr. Tang also directs CC's seven-bed Clinical Research Unit.

MetroHealth System: MetroHealth, Cuyahoga County's safety net hospital, is an integrated health system with an acute care hospital housing the area's only Burn Center and a Level 1 Adult Trauma Center. The Emergency Department is among the busiest in the country (>275 visits per day); Metro Life Flight air ambulance service is internationally recognized. Not surprising, then, that the MetroHealth Trauma Research Institute of Cleveland (MeTRIC) is one of MH's research strengths. MH is also the home base of the CWRU SOM's Center for Reducing Health Disparities (led by Dr. Sehgal, *Hub Research Capacity*), the Center for Health Research and Policy, and the Better Health Partnership, a PBRN that has functioned as a citywide learning health system. MH has strong research programs in renal disease, perinatal medicine, rehabilitation medicine, and health services research. Perinatal research is led by *Hub Research Capacity PCI* lead Dr. Catalano, who also directs the MH Clinical Research Unit. MH maintains dedicated C/T space (80,000 sq ft) and is constructing special facilities for the program in functional electrical stimulation (FES). MH was the first of the CWRU-affiliated hospitals to establish a formal research track in its internal medicine residency and is committed to C/T research training. MH was the first public safety net hospital system in the U.S. to install an electronic health record (EHR) for clinical care (1999), and has been recognized by several national organizations for its early adoption and sustained value of its EHR. Over 40% of MH's socioeconomically diverse patient population is enrolled in Epic's MyChart personal health record. MH actively mines the EHR with Explorys for research studies. Dr. Kaelber, Chief Medical Informatics Officer and Vice President of Health Informatics at MH, is the founding director of the Center for Clinical Informatics Research and Education, and directs one of only a few ACGME accredited fellowship programs in Clinical Informatics. Other CTSC leadership from MH includes Drs. Sedor (*Translational Endeavors*) and Einstadter (*Research Methods*).

University Hospitals (UH): University Hospitals is a major hospital system in Northeast Ohio, serving patients through an integrated network of hospitals, outpatient centers, and primary care physicians. UH Cleveland Medical Center (UHCMC) is the academic medical center for the system, and shares its campus and research space with the SOM. UHCMC includes Rainbow Babies and Children's Hospital, among the country's most respected children's hospitals and internationally recognized for its care and research in neonatology (USNWR #4 in US) and cystic fibrosis (USNWR Pulm #8 in

US); MacDonald Women's Hospital, the only dedicated hospital for women in Ohio, and the Seidman Cancer Center, associated with the our NCI designated Case Comprehensive Cancer Center. UH has an internal medicine residency research track that is now aiming at attracting CWRU MSTP graduates to reduce time to independence. Strong research based at UHCMC, together with collaboration with SOM basic science departments, has increased collaborative (P and U) grants greatly over the last decade. The clinical home of the SOM's NICHD Neonatal Research Network resides at Rainbow, and the NINDS SUDEP Center resides at UHCMC. UHCMC is also the home of the Harington Discovery Institute (HDI), which supports physician-scientists regionally, nationally, and internationally for drug discovery and translation to the commercial sector. Established in 2012, the HDI has funded 79 drug development projects; six have resulted in spin-off companies, of which three have been sold to major pharmaceutical companies. The UH Clinical Research Center, Directed by Dr. McComsey, oversees the clinical research programs at UHCMC, and is the home for the CTSC *Regulatory Knowledge Support (RKS)* section of the *Research Methods* component. *RKS* operates an IND/IDE Core to assist investigators in preparing, submitting, and managing INDs and IDEs. Dr. Cola, previous Vice President of the UHCRC at UH and now at the Weatherhead School of Management at CWRU, leads RKS for the CTSC. The 10-bed Clinical Research Unit at UHCMC, also directed by Dr. McComsey, supports not only clinical trial participation for UH, but provides bionutrition support and specialized laboratory assays for the CTSC. In addition to Drs. McComsey and Cola, other CTSC leadership based at UH includes Dr. Chmiel, who leads *Network Capacity* and is the LTIC lead. Dr. Konstan is Vice Chair for Clinical Research for pediatrics at UH.

Louis Stokes Veterans Administration Medical Center (VA): The Louis Stokes Cleveland VA Medical Center is one of five facilities constituting the VA Healthcare System of Ohio. Care is provided to eligible veterans from 24 counties in Northeast Ohio covering more than 105,000 Veterans each year. Our VA has seven Clinical Programs of Excellence, more than any other VA medical center in the country. As a clinical affiliate of CWRU SOM, the VA actively supports medical education training programs and broad-based research initiatives. It has a large, well-funded research and development program including studies in: Biomedical Research, Health Services Research, Rehabilitation Research, Clinical and Cooperative Studies, and Million Veteran Program. It is an active participant in the VA Cooperative Studies programs, which are large scale, clinical research studies on health issues vital to our nation's Veterans. The VA's Rehabilitation Research and Development Service (RR&D) recognizes two Centers of Excellence at our VA: The Center for Advanced Platform Technology (APT), which is developing advanced technologies that serve the clinical needs of Veterans with motor and sensory deficits and limb loss, and The Center for Functional Electrical Stimulation (FES), which is investigating a technology that relies on controlled electrical current to activate paralyzed muscles to return full or partial physical function to individuals with disabilities. Accomplishments include FDA approval of a hand grasp system and commencement of clinical trials of an advanced bladder/bowel management system. A strong working partnership has allowed the CTSC to support KL2 level scholars based at the VA in novel ways, as well as capitalize on the expertise at this site.

Other CWRU Schools: The Case School of Engineering (CSE) contributes strongly to the CTSC in computer science and biomedical engineering. The Department of Biomedical Engineering (BME), a joint department of the SOM and CSE, is consistently ranked among the top 20 BME departments by *USNWR*, with special expertise in imaging, materials science and drug delivery, and neuroscience and FES. *Informatics* and our training programs benefit from the department of electrical engineering and computer sciences, and many TL1 scholars train in BME. **The Frances Payne Bolton School of Nursing** (**SON)** ranks in the top 10 US nursing schools (USNWR, 2016), and contributes many KL2 Scholars and faculty educators to the CTSC. **The Mandel School of Applied Social Sciences (MSASS)** ranks in the top 10 in the US. It maintains the NEO CANDO database for Cleveland, which maps indicators of poverty in the neighborhoods. This database will be coordinated with the CLEARPATH database being developed from EHR data in our *Informatics* component. Faculty from the **Weatherhead School of Management** teach the KL2 scholars and the **College of Arts and Sciences and the School of Dental Medicine** have contributed successful KL2 scholars. Faculty from the Law-Medicine Center, **School of Law,** participate in our bioethics program. So, all eight schools at CWRU participate in the CTSC.

Totality of the program: Thus, all of the partners of the CTSC contribute to this complex research ecosystem based in a clinical care system that serves 90% of the Cleveland area population by using both their own special strengths and common support systems. Leadership of the CTSC is drawn from all participating entities, where all of the leaders and investigators are faculty members at CWRU. Over the last decade we learned to share specific resources seamlessly across partner institutions, to generate enthusiasm for multi-institutional and multi-disciplinary research by encouraging team science, and to utilize technology to keep communication fresh and to celebrate our opportunities to work with one another. Every year, new collaborative programs emerge – so far

in 2107 a trans-city Alzheimer's Center has been assembled. The Better Health Partnership now includes primary care practices from CC, MH, UH, and other hospital systems in Northeast Ohio. And we have established new collaborations with many CTSA Hubs (described below).

Aim 2. Collaboration and Communication

Engaging with CTSA network activities: The Cleveland CTSC is committed to actively participating in CTSA network activities. The PI, Dr. Konstan, regularly attends the annual PI meeting, and presented the Lifespan DTF update at the April 2016 PI meeting. He attends the monthly CTSA PI calls, and listens in on the monthly Steering Committee calls, as well as joining our Hub Pod calls. The information garnered from these meetings, calls, and other sources from NCATS are shared with the CTSC Steering Committee and Executive Committee, and, when appropriate, to the broader CTSC research community through our Hub's monthly newsletter. Bi-directional flow of communication between our CTSA Hub research community and the Steering Committee and other CTSA network committees will continue to be facilitated through our Executive Director. The CTSC is eager to contribute in other ways to CTSA network activities, including an opportunity to serve on the CTSA Steering Committee and other committees/work groups established by NCATS and the CTSA network. Dr. Davis served on NCATS Council 2012-2016.

Domain Task Forces**:** Our Hub actively participates in the five CTSA Domain Task Forces (DTFs), with CTSC leaders identified for each DTF (Table 4). Our most recent example of DTF participation is with the Lifespan DTF Single Disease Workgroup. Dr. Konstan co-organized an NCATS webinar on March 9, 2016 titled "Lifespan Approach to Rare Diseases," and presented "Cystic Fibrosis across the Lifespan," in an effort that involved five other CTSA Hubs.

Table 4: Domain Task Forces Representation (DTF)

Workforce Development	Raed Dweik, MD
Collaboration/Engagement	Elaine Borawski, PhD
Integration Across the Lifespan	Michael Konstan, MD
Methods/Processes	Wilson Tang, MD
Informatics	Mitchell Krieger, MD

Collaboration with other CTSA Hubs and other national networks: As noted in the Overall section, the three CTSA Hubs in Ohio have established several collaborations, including partnering to form the Ohio Clinical Trial Collaborative in 2013. The OCTC offers economies of scale and capacity, leveraging expertise to facilitate clinical trial efforts across the state. Most recently we submitted a combined proposal for the Precision Medicine Initiative. The three Ohio CTSAs also forged an IRB reliance model, expanded from the successful reliance initiative at the Cleveland Hub among our hospital partners to encompass eight legally separate Ohio institutions. We disseminated our experience to other Hubs nationally; the Cleveland CTSC was one of eight CTSA Hubs to participate in the reliant IRB project which created IRBRely (Dr. Cola serves on the Executive Committee). We are currently one among 12 Hubs participating in the Scientific Review Committee pilot led by the Tufts CTSA Hub. We recently were invited by NCATS to submit a full U01 application for a CTSA Collaborative Innovation Award based on a favorable review of our X02 pre-application "Inter-CTSA Training Program in Translational Practice-Based Research Methods" with the CTSA Hubs at the University of Cincinnati and Oregon Health & Science University. This collaborative will include six to eight CTSA Hubs. And we have proposed several collaborative initiatives in this application with: 1) University of Washington CTSA (see *Hub Research Capacity* and *Network Capacity*), 2) University of Cincinnati and UC Irvine CTSAs (for evaluating KL2 scholars, see letters of support), and 3) A multi-hub collaboration with Weill Cornell, UW Madison, Einstein and Johns Hopkins (development and dissemination of methodology regarding case studies of successful C/T research, see letters of support). We also actively collaborate with national C/T networks, both NIH and foundation supported, as noted in the Overall section, and participate in PCORI projects and PCORnet (e.g. ImproveCareNow). We are engaged with PCORnet leadership to increase our collaborative activities, via Dr. Jennifer DeVoe, a member of our EAC, who directs development of the PCORnet CDRN (ADVANCE). These regional and national collaborations highlight our ability to effectively collaborate and communicate with one another, both internally and externally. We have been successful in managing competing institutional perspectives, differences in institutional culture and resources, and sharing of institutional expertise and resources among the five partner institutions in our Cleveland CTSA Hub, as well as state-wide and nationally. Within our own Hub, we believe having leadership representation on all research components and training cores from all partners, all of whom share faculty appointments at the SOM, has been crucial to this success.

Collaborative Leadership and Communication Plan with Training Components: A collaborative leadership model has been developed to promote synergy between the U, K and T Award leads. Within the organizational structure of the CTSC, the directors of the two Training Cores (Dr. Dweik for the *KL2* and Dr. Harding for the *TL1*) are fully integrated: the KL2 director is a TL1 associate director, and the TL1 director is a KL2 associate director, and other Training Core leaders (Drs. Shirley Moore and James Spilsbury) are associate directors for

both programs. There are many shared resources, including mentors and curriculum, among these two programs by design (See sections I. and J. for details). The PI of the U (Dr. Konstan) is a member of the TWD Advisory Board, which is also a subcommittee within both training cores (K and T), providing direct communication among the U, K and T. The Executive Committee provides the main source for collaborative leadership between the two training cores (*KL2* and *TL1*) and the six research components of the U, given that the eight leaders of these components and cores, along with the executive leadership and chairs of the SRC and TWD and Child Health advisory boards meet monthly as a group, a meeting frequency that provides much opportunity for integrating the educational and training programs of the CTSC in C/T science with all five partner institutions.

Aim 3: Evaluation and Continuous Improvement

CTSC Program Evaluation integrates data tracking and evaluation for all CTSC research components and training cores, and incorporates a utilization-focused, participatory, and methodologically flexible approach which is based on the CDC Framework for Program Evaluation and the American Evaluation Association Program Evaluation Standards.[1,2] In close collaboration with the CTSC executive leadership and EAC, we apply evaluation processes and findings to priority-setting, program accountability, and continuous improvement (CI), facilitating Hub data collection and evaluation efforts across the CTSC. Our evaluation system uses both qualitative and quantitative data. All components and cores share responsibility for collecting process and results data and contributing to development of meaningful metrics to assure achievement of their goals and measuring program impact. Members of the CTSC and EAC regard evaluation findings as the objective basis for determining progress and CI in response to issues raised during the EAC visit and in the EAC report. We are actively involved in all levels of CTSA evaluation, from national to community-based. Nationally, we participate in collaborations with several other CTSA Hubs to apply innovative approaches to evaluating CTSA Hubs (see Aim 2). We collaborate with community-based researchers on developmental evaluation approaches to assess outcomes and impacts of community-based research.[3]

Program Evaluation is directed by **Clara Pelfrey, PhD**, from the SOM Center for Medical Education. She has served as our Evaluation Director since 2012, and has 27 years of experience in translational research, scientific review and teaching. Dr. Pelfrey is President of the Translational Research Evaluation Topical Interest Group (TRE TIG) for the American Evaluation Association. Dr. Pelfrey is a member of the Methods & Process DTF and the Institutional Readiness for Team Science working group. Clara works closely with Dr. William Trochim, who co-leads the CTSA Evaluators Group and the NCATS Methods & Process DTF. To assure that the CTSC is kept abreast of developments in CTSA metrics, Dr. Clara Pelfrey serves as the CTSC project manager for the NCATS Common Metrics Implementation. She oversees and coordinates the CTSC Common Metrics teams and reports monthly to leadership and to our NCATS Program Director.

External Advisory Committee (EAC) and Responsiveness of CTSC to EAC Recommendations: The EAC members are listed in Table 2, and have been selected in part on their ability to contribute to our continuous improvement program. The EAC reviews CTSC programs and progress at a one-and-a-half-day day annual meeting. One month in advance of the visit, the EAC receives a written report which includes summaries and highlights from the annual progress report to NCATS, as well as topics chosen to provoke change if needed. The meeting agenda is determined by the EAC and includes a summary of responses to the previous EAC review plus corrective actions. The EAC provides a final report detailing the strengths and weaknesses of the CTSC plus recommendations to enhance support of the programs. The CTSC PIs and Executive Committee address comments in the EAC review promptly and confirm appropriateness of the corrective interventions with the Chair of the EAC. Notable changes made by the CTSC in response to EAC feedback are shown in Table 5.

Table 5: Notable changes made by the CTSC in response to EAC feedback

1.	Successful implementation of the Rockefeller University Graduate Tracking Survey System to systematically track KL2 Scholar career progression and outcomes.
2.	Reorganization and redesign of technology core facilities access and processes via a school-wide core management system, such that requests, use, billing and tracking will be standardized and centralized.
3.	To save costs and increase efficiency, chargeback mechanisms have been instituted in the CRUS such that as of 7/1/2015, all investigators must include full CRUS costs in their application budgets and must work with CRUS to improve study design.
4.	Used KL2 feedback to improve the training experience by the addition of training in entrepreneurialism and grant writing skills and exposure to study section review processes.
5.	To support faculty in the use of Translational Technology Resources, a re-organization of core facility website and structure resulted in institution of a core facility management system. And a Regulatory Support and IND/IDE Core were established.
6.	EAC membership expanded to include academic-industry partners and a chronic disease research participant.
7.	CTSC highlights successes via a monthly email newsletter to members.
8.	The CWRU SOM appointment, promotion & tenure policy was changed to recognize and reward investigators who engage in team science; this policy was adopted and undergoing full implementation by Nursing, Dental and other CWRU schools.

Data Integration and Commitment to Continuous Improvement: Management of continuous quality improvement depends on standardized data input and commitment to improvement from all CTSC members. We have designed relevant process and outcome/impact data collection tools for each of the research components and training cores, and for our technology service cores. Our evaluation model focuses on implementation of the CTSC program as designed, and its outcomes and impact. Component services usage data are collected quarterly and the data are integrated centrally in the Request Management System (RMS). Investigators can place a request for services directly through RMS, where our Research Concierge triages the requests and assigns component experts to consult with the investigator. Investigators benefit from face-to-face consultations with the Research Concierge, who successfully matches their specific needs with the correct component experts (e.g. biostatisticians or community-based researchers). RMS allows multiple experts to be assigned within the same project, facilitating our ability to visualize a collaborative network of experts working on any single project. We have published the use of RMS to examine cross-disciplinary collaboration.[4]

CTSC process improvement: streamlining access to component services and centralizing billing and reporting. Thanks in part to investigator feedback and CTSC input, the CWRU SOM is engaging in a multi-year process to improve efficiency and provide accountability by streamlining investigator access to all technology core facilities and by centralizing billing and reporting by the core facilities. Three Core Facilities Retreats have been conducted during the last four years with demonstrable improvements in their services. These improvements have culminated in the creation of a Core Advisory Committee, standardization of the process for creating new and renewed current cores, development of a strategic plan for cores, enhancement and consolidation of the Core Facilities website, publication of newsletters with core scientific achievements and the creation of a Best Practices Manual for Core Operations. During the next funding cycle, the CTSC will take a major step forward when we implement the CWRU SOM-wide core management system. Once installed, this system will provide institution-wide core facility access. CTSC components will be integrated into this system and as the CTSC web-based service portal, investigators will be able to use a single web-site to request a wide range of services, which will allow for seamless integration of resources. This model of a single portal to request all core/component resources greatly expands the types and quantity of resources that will be available to investigators, providing “one-stop-shopping” for easy access. Our data collection has exceeded approximately 80% for each core with our existing system, but will be much improved with a CTSC system-wide standardized management system, using electronic data input tied to responses to core service requests from each investigator. Additional benefits are that both billing and investigator follow-up for satisfaction can be centralized into a single data warehouse. Publications and grants that result from collaborations with core experts can be identified much more readily by triggering automated PubMed searches and investigator queries. We plan to use this powerful new data source to engage in experimental approaches to examine the effect of providing/not providing monthly investigator feedback to the leadership of components and cores. Outcomes will measure resulting changes in service provision and implementation of innovative solutions in the components and cores.

Evaluating CTSC Researchers. CTSC membership is open to anyone including students, trainees, fellows, research staff, faculty and community members. We currently have over 5000 members including more than 200 who are members of the community or other academic institutions. Members may access services by completing a short biographic form that creates a profile in the CTSC membership database. The information collected includes basic professional and demographic information and also makes it easier to track member information in a variety of databases throughout the CTSC institutions, including the faculty portfolio database, Pure Experts and the IRB databases, among others. A powerful new resource just made available to us is the Pure Experts Reporting module and dashboard. Based on the NCATS Common Metrics project and validated measures of investigator productivity and collaboration, in Pure Experts we define performance metrics including publication trends, field-weighted citation analysis and trends, collaboration patterns, top journal titles, top researchers and h-indices. Likewise, we can generate progress reports on our KL2 Scholars, our Pilot awardees and other specific research groups of interest. The ability to integrate data from several authoritative sources increases data validity and reduces the requirement to constantly collect and update primary data. We have an extensive capacity to collect data including reports, validated surveys and databases (Table 6), demonstrating our capacity to collect comprehensive, theoretically based data to evaluate impact. These data will be supplemented with data from a variety of other sources to provide a multi-dimensional picture of the CTSC operation and its impact.

Table 6: CTSC Data Sources		
Reports/Summaries	**Surveys**	**Databases (cont.)**
• Annual Progress Reports	• Course/workshop evaluations	• Pure Experts reporting module
• Applicant information	• Investigator surveys/feedback	• NIH Reporter
• CWRU grants management	• Graduate Tracking Survey System	• TTI*, Regulatory and FDA support databases
• KL2 Career Development Plan	• KL2 exit interviews & surveys	• Reliant IRB database
• KL2 Scholar CVs	• Mentoring questionnaire	• IND/IDE core database
• Pilot awardee annual reports	• Key informant interview data	• PubMed
• Research Concierge usage	• Redcap Surveys	• My Bibliography
• CTSC letters of support	**Databases**	• Webgrants- application, scientific review
• Presentations to/with community	• Request Management System (RMS)	• ICB* tracking databases (SHED, CLEARPATH, etc.)
• Case studies: success stories	• Program databases (KL2, TL1, etc.)	• Community Researcher training program databases
	• Pilot program tracking database	• Community research consult service tracking system
*Abbreviations: ICB- Institute of Computational Biology; TTI-Translational Technologies & Innovation		

The Component Metrics: Each of the research components and training cores has requirements for program evaluation and outcome metrics. The Evaluation Program works with the Executive Committee and the component/training core leads to select appropriate tools and processes to collect data related to a prospectively designed plan for tracking, analysis, and continuous process improvement. As much as possible, the data will be part of the ongoing operation of the component services. Each component/training core will be responsible for providing the necessary resources to initially collect evaluation metric data that are not captured as part of CTSC operations. Where needed, the Evaluation Program will provide expertise and resources to facilitate the collection of data. Performance Indicators and Key Milestones are presented in each component and training core section in this application. Progress on the NCATS Common Metrics to date are also presented.

AIM 4: Quality and Efficiency

The Cleveland CTSC strives for outstanding quality and efficiency in C/T research. Our CTSC is committed to and will ensure 1) ethical research designs, 2) minimization of risks to participants, 3) feasibility of study accrual and performance, 4) accurate study conduct and timely closure, and 5) prompt, meaningful, and comprehensible reporting to the participants, the scientific community and the public. Given our commitment to quality, safety and efficiency, this program will be directed by **Charlotte Bhasin, MOT, OTR/L,** who has extensive experience as a healthcare director, a clinician, and a key administrator managing clinical and translational research at the CTSC since its inception.

Advancement of safety and ethical conduct in clinical studies, essential to high quality clinical and translational research, will be obtained by assisting investigators, organizations and participants to identify and minimize risks and plan accordingly. We are familiar with and work closely with relevant Institutional Review Boards (IRBs) having an active role in the Reliant IRB Process (see Regulatory Knowledge), forming a core of ethical standards. All CTSC partner institutions have robust research compliance programs and offices, and offer a full range of training on compliance topics (see box at right). Our Research Subject Advocates (RSA) also ensure that participants are fully engaged and familiar with details of the trials/studies. A recent example of the careful approach to safe and ethical conduct of a high-risk study was the mesenchymal stem cell transplant trial in multiple sclerosis patients. The study, and particularly the study subjects benefitted greatly from intense discussions and inter-institutional collaboration, with considerable input from the SRC, RSA, and IRB.

All CTSC partner institutions have robust research compliance training, covering topics such as:

- **The Scientist as a Responsible Member of Society**
- **Conflict of Interest Disclosures**
- **Safe Laboratory Practices**
- **Human Subjects Protection**
- **Mentor/Mentee Responsibilities**
- **IND/IDE processes**
- **Collaborative Team Research**
- **Peer Review**
- **Responsible Conduct of Research**
- **Data Acquisition, Management**
- **Research Misconduct**
- **Responsible Authorship & Publication**

Ethical Concerns. Well-established and widely accepted ethical concerns are normally addressed by careful protocol construction by a trained and credentialed research team, followed by scientific review, statistical design review, and the IRB. Verified understanding and ongoing acceptance by the research participant, including updated information about the risks of the clinical trial as it emerges are the responsibility of the research team and the RSA. The team is responsible for developing suitable methodologies for creating and implementing an ethical plan for a study under unusual conditions such as 1) novel or unknown risks such as those associated with gene therapy, 2) impairment of comprehension such as associated with altered states of consciousness or lack of intellectual development, 3) awareness of potential hazards of unknown risk such as associated with genetic family studies. Our method for handling issues of this sort is to develop a team approach including all those involved in the study, experts in ethics, clinical trials, and members of the community and to recruit a

clinical trials nurse, a social worker, and a member of the research team to fully inform participants and document comprehension over an extended period of time.

Feasibility is determined for CTSC research studies by employing uniform systems and processes across our CTSC partner institutions. During protocol development, investigators complete forms and employ checklists, all of which are subject to review. In addition, an electronic assistive resource is available to ascertain actual numbers of eligible individuals accessible to the investigators (see *Hub Research Capacity*). Feasibility planning and assessment requires an upfront evaluation of the capacity of the study plan and operational procedures to fulfill the scientific, regulatory, medical, and ethical requirements of the protocol. Our Quality and Efficiency Program monitors and evaluates the activities of trial planning and performance with assistance from *Hub Research Capacity* and *Network Capacity*.

Recruitment. Recruitment for all studies is assessed by the Participant Recruitment Specialists (PRS) of *Hub Research Capacity*, who advocate and assist in the inclusion of special populations. When needed the PRS collaborate with investigators to modify protocols and/or recruitment strategies and can identify a PRS or a Point-of-Contact for Special Populations at partner institutions. The PRS will identify and build a cadre of relationships with points-of-contact leaders– in pediatric and geriatric research, rare diseases, minority recruitment, and other special populations, in order to innovate in recruitment methodology and broaden applicability of results to diverse populations.

Completion and Closure of Clinical Research Studies. The CTSC serves as the responsible steward of the portfolio of C/T research. After clinical trials are completed and the data analyzed publication should be prompt, even if the study revealed no new evidence of toxicity or activity. Participants and the public are entitled to be published based on their expressed interest in helping clinical science find better ways of managing diseases. The CTSC will encourage and provide assistance, if required, to assure Clinicaltrials.gov is routinely updated and that results and outcomes are reported irrespective of peer-reviewed publication status. Publications from trials will be widely disseminated through public health lectures and public access websites, particularly via the health information website, NetWellness, supported by the three CTSA Hubs in Ohio.

Study Drug Management. Regulatory standards are upheld across all our clinical partner institutions with the highest standards and procedures in place regarding ordering, dispensing and administering any study drug. Research pharmacy services are specialized to provide the needs and regulations of studies involving research agents.

STRICT STUDY DRUG MANAGEMENT PLANS ARE IN PLACE:

- ✓ Pharmacy receives and stores study drug under adequate security and controlled temperature conditions.
- ✓ Study drug dispensed by pharmacy as required by the protocol while adhering to applicable local and federal requirements.
- ✓ Drug accountability recorded compliantly with federal regulations.
- ✓ Study drug supply is used for a specific protocol and not for any other purpose.
- ✓ Pharmacy dispenses drug for protocol that is IRB approved.
- ✓ Pharmacy ensures that only authorized investigators prescribe the study drug.
- ✓ Pharmacy ensures that only subjects who provided informed consent receive the study drug.
- ✓ Study team cooperates with routine monitoring by pharmacy of study drug policies and procedures.
- ✓ Pharmacy returns unused study drug or destroys drug onsite, according to sponsor.

Quality Assurance processes run parallel across our CTSC institutions with system-wide approaches to assure that quality research is initiated, conducted, disseminated and closed in the highest quality manner. Quality Assessment (QA) reviews, both routine and unscheduled, are conducted on research studies at each CTSC institution to ensure the protection of human subjects, data integrity, and compliance. These reviews are extensive and cover regulatory documentation, IRB documentation, subject recruitment procedures, the ongoing informed consent process, participant eligibility assessment, adverse event reporting, protocol deviations, drug/device dispensing and accountability, data collection and source documents.

Continuous Quality Improvement. Using CTSC project management practices of prioritization, implementation planning, milestone tracking, and enhanced communication strategies, the hospital partner's CRUs increased implementation of high acuity protocols by 49% over the past 2 years. Our success with this strategy supports the feasibility of extending the project management practices to multi-site clinical trials and pilot projects.

In summary, although significant and appropriate procedures are established at institutional levels for quality research, this application provides the CTSC a tremendous opportunity to provide integrated, hand-on resources for investigators to conduct high-quality human research, building a foundation that promotes quality, efficiency, collaboration, and ultimately success in project implementation and study execution.

B. Informatics

SPECIFIC AIMS

Informatics is critical for the successful capture, management, analysis, and interpretation of clinical and translational data. The informatics needs of CTSC investigators include the translation of data into information and then into knowledge by combining basic research (e.g. proteomic profiles, biomarkers, genome sequences), clinical research (e.g. clinical trials, EHRs), and population research (e.g. community interventions). The primary goal of the *Informatics* component and its Biomedical Informatics Team (BIT) is to provide a stable, flexible, comprehensive, and user friendly biomedical informatics infrastructure (tools, processes, people, and training) that enables and enhances all aspects of translational research.

Aim 1: Provide Informatics tools to support and accelerate clinical and translational research. Our CTSC BIT has had considerable success in developing and deploying informatics tools to enable clinical research with the numbers and users of CTSC supported biomedical informatics-related projects increasing 2-3 fold in the past five years (Table 1). The BIT will provide infrastructure to aggregate and integrate data from cells to society in appropriate formats in a timely and efficient manner. We will expand and extend the use of existing tools for data capture, management, and discovery. We will leverage our multi-institutional investment in the Institute for Computational Biology (ICB), which has developed a data management infrastructure that can reliably and securely integrate data for individual research projects (SHED) while deploying a Cleveland-wide EHR database for research (CLEARPATH). We also expand use of our successful Cleveland-innovated Explorys tool which includes over 50 million lives including all patients seen in Cleveland healthcare institutions. We will measure success by increases in studies supported, number of data sources successfully integrated, and the number of resulting discoveries and publications. Best practices will be promoted through our existing and emerging tools that address the increasing complexity and sophistication of data capture, management, analysis, and interpretation. For the researcher, initiatives will focus on enhancing innovative tools to identify, enroll and facilitate ongoing engagement of participants. For participants, providing results and interpretation, whether privately or in aggregate, will be performed using developing national standards. Our success will be measured by increases in projects, enrollment & retention of participants, and usage of biomedical informatics tools and resources.

METRIC	2012 (baseline)	2013	2014	2015	2016
REDCap (CCF, MHS, UH)					
# of unique users	365	486	604	814	951
# of unique projects	405	527	688	769	849
Explorys (CCF, MHS, UH)+ [*Slicer/Dicer]					
# of unique users	236	271	301	496*	718*
# of unique queries	9,998	13,395	14,127	14,280	5,411

Table 1: Summary data 2012-2016
*notes data combining users and queries from Explorys + Slicer/Dicer.
Note 2016 data on queries is reduced due to a change in reporting queries

Aim 2: Educate and train researchers, trainees, and staff in biomedical informatics tools and resources. Informatics tools and resources are in constant flux, creating a training challenge for the informatics naïve and a maintenance challenge for those already trained. The BIT will provide training through "studios" to discuss and demonstrate use of specific tools and support informatics-related study design. The BIT is expanding formal educational opportunities for certificates, masters and PhD degrees in informatics and launched an ACGME-accredited Clinical Informatics fellowship program that will be city-wide. Our success will be measured by the increased number of informatics consults, attendance at studios, and the number of investigators who work in clinical & translational science.

Aim 3: Enable collaborative research and data sharing within the CTSC and across the nation. Collaboration among basic, clinical, and translational researchers requires communication and access. Locally the BIT will encourage collaboration through the use of standardized informatics tools (e.g. REDCap, SHED, I2B2, SHRINE) and sharing of study-specific meta-data. Nationally, the BIT will monitor progress and implement processes to standardize research data (e.g. common data models, the BD2K initiatives, BioCADDIE, NIH Data Commons, TriNetX, sharing mechanisms [APIs], federated data queries). Collaboration with the community will be fostered through social media and mobile devices. Success will be measured by the increased use of standardized measures and tools and increases in collaborative studies.

Component Lead: This component will be co-led by **Jonathan Haines, PhD,** director of ICB and Chair of the Dept of Population & Quantitative Health Sciences, **David Kaelber, MD, PhD, MPH, FACMI**, chief medical informatics officer of the MH, and **Mitchel Krieger, MD, FACS**, Associate Chief Information Officer, CC.

Informatics

Goal: The progressively routine acquisition of data of different scales and types in the basic, clinical, and translational biomedical sciences has created numerous opportunities and challenges for both physicians and research scientists to capture, manage, analyze, and interpret these data, especially in an integrated fashion. The overall goal of the *Informatics* component and its Biomedical Informatics Team (BIT) is to provide a stable, flexible, comprehensive and user-friendly biomedical informatics infrastructure (tools, processes, people, and training) that serves to accelerate clinical and translational research across the CTSC. The BIT provides access to expertise in all aspects of biomedical informatics, including information technology, medical informatics, and bioinformatics. We will leverage the existing extensive EHR and research informatics infrastructures at the participating institutions, and integrate these existing and emerging data capture and management systems with new resources established in the Institute of Computational Biology (ICB), a multi-institutional initiative of CWRU, CC and UH headed by Dr. Haines. Concurrently, the affiliated hospital systems continue to increase their ability to capture and use EHR data to support translational research directly at the point of patient care. Use of these expanded and increasingly sophisticated tools is essential to achieving our goals, requiring an active informal and formal education and training environment. The tools and processes implemented and coordinated by the BIT (Table 2) are constantly under review and refinement. As described below these tools and processes have an impact across many CTSC components and drive collaboration around the world.

Program Leadership: This program will be led by **Jonathan Haines, PhD**, Director of the ICB and Chair of the Department of Population & Quantitative Health Sciences at CWRU SOM, **David Kaelber, MD, PhD, MPH, FACMI,** CMIO at MH, and **Mitchel Krieger, MD**, ACIO at CC. Dr. Haines's broad experience in biomedical informatics is complemented by both Drs. Kaelber and Krieger, who have been directing medical informatics efforts for the CTSC at MH and CC, respectively. The Co-leads confer weekly, will hold quarterly meetings of the BIT and regularly report out Informatics component activities at Executive Committee meetings. Other key BIT members include: **Jeffrey Sunshine, PhD, MD**, CMIO at UH. **Rong Xu, PhD**, an expert in using EHR data to identify novel disease processes, adverse drug outcomes and interactions; **Dana Crawford, PhD** an expert in defining and refining disease phenotypes using EHR data and **Satya Sahoo, PhD** an expert in high throughput EHR data capture with a particular interest in provenance of metadata. Drs. Xu, Crawford, and Sahoo will provide leadership in developing and applying novel tools for data integration.

Tool Usage: Existing tools that facilitate research (e.g. Pure Experts (formerly SciVal Experts), eResearch, IRB-hub, Webgrants, and ResearchMatch), access data (e.g. Explorys, SHED, CLEARPATH, I2B2, SHRINE), collect additional data (e.g. REDCap), and manage these data (e.g. SHED) will be supported and refined by the BIT. Over the past five years, CTSC support has resulted in a 260% increase (to >950) in REDCap users and a 210% increase in REDCap projects (to >850). Similarly, the number of Explorys users has increased by 75% (to 412) while the introduction of Epic's Slicer-Dicer in 2015 (now 300 users) and the SHED (>1000 users) have also contributed significantly to accelerating CTSC research. EHRs are active in all of the hospital system affiliates. CC (Epic), UH (Allscripts), and MH (Epic) already share some EHR data through a state-wide EHR exchange system (CliniSync), while the CC and MH systems can share patient records through Epic's CareEverywhere health information exchange. The increased use of these tools have resulted both from the rise in interest from translational scientists and the growing number and size of data sources. In aggregate, over one-third of full-time affiliated faculty have used the CTSC biomedical informatics resources.

BIT Resources			
Name	**Type**	**Description**	**Component Usage**
CETHI	Process	Manages formal educational programs	KL2, TL1
CLEARPATH	Tool	Integrated EHR data warehouse	HRC, NC, RM, C&C
Consults	Process	Provide access to tools and processes	All
COSMOS	Tool	National EPIC data warehouse	HRC, NC
eResearch	Tool	Access to local EPIC data warehouse	HRC, NC
Explorys	Tool	Commercial EHR data warehouse	HRC, NC, RM
I2B2	Tool	Front end access to EHR data	HRC, NC
IRB-Hub	Tool	Administrative management	TE, HRC, NC, RM, C&C
Knowledge Program	Tool	Patient reported outcomes	C&C, HRC, NC, RM
MyChart	Tool	Patient reported outcomes and patient access to EHR data	C&C, HRC, NC, RM
Online Tutorials	Process	Self-directed education on tool usage	All
Pure Experts	Tool	Faculty research database	All
REDCap	Tool	Data acquisition and Surveys	All
ResearchMatch	Tool	Cohort development	C&C, HRC, NC, RM
SHED	Tool	Integrated data management for individual research studies	All
SHRINE	Tool	Cross institutional data sharing	C&C, HRC, NC
Slicer-Dicer	Tool	EPIC EHR data query	HRC, NC, RM
Studios	Process	Provide face-to-face training and consultation	All
TriNetX	Tool	Cohort development tool for clinical trials	HRC, NC
Tool Development	Process	Develop/refine tools for specific research needs	All
WebGrants	Tool	Administrative management	Admin, C&C, TE

Table 2: Informatics tools: definitions and interactions.

Adaptive Data Organization and Learning Healthcare System: The rapid evolution and successful use of biomedical informatics data requires constant innovation. To maintain strong and secure clinical data capture

and management, our current approach toward biomedical informatics is a distributed model, with each of our affiliated institutions maintaining its own resources, however the CTSC provides interconnections and synergies that would otherwise be lost. This mirrors the situation nationally, with its attendant challenges in maintaining security and privacy while promoting data sharing and collaboration. The CTSC serves to coordinate these activities by providing consistent data capture and management servers at each site. Moving forward, we will leverage this approach and add increasing resource integration resulting in an efficient hybrid between a federated and centralized biomedical informatics structure.

An example of our recent efforts in this area, the ICB launched the SHED (*S*afely *H*eld *E*lectronic *D*ata) tool in July 2015 to manage data centrally for investigator-initiated studies. SHED can capture, store, aggregate, reconcile, and manage a variety of types and scales of data. The SHED manages these studies individually, but, by using common data models, promotes **queries across the aggregate data** that foster intra- and inter-institutional collaborative efforts by identifying existing data and samples useful for future studies. The SHED was initially validated in the context of 45 studies. Now in its second year, and with the transfer of all Case Comprehensive Cancer Center (CCCC) clinical trials data, SHED now contains over 1,050 studies enabling investigators to integrate their clinical data in novel and secure ways that were previously impossible. Going forward we will enable data capture through other systems (e.g. REDCap) to be migrated to the SHED to further accelerate data integration across studies.

A critical CTSC-supported approach uses tools from Explorys, a spin-out company from CC that is now part of IBM-Watson Health. Explorys makes available a cloud computing platform that extracts structured EHR data from multiple healthcare providers. This platform is actively used by all in our CTSC and across the USA. It has been important to *Hub Research Capacity* and *Community and Collaboration* projects. **It contains structured data from 360 hospitals (including Cleveland CTSC hospitals), 315,000 providers, and over 50 million patient records**. The platform is specialized for scalable and cost-effective access. It employs a standardized data curation process using well-established ontological and terminological systems including SNOMED, ICD-9, ICD-10, ICD-O, CPT, LOINC, demographic, and pharmaceutical classifications. In this context Explorys (and Slicer-Dicer etc.) are important tools for participant selection.

A third example of our efforts, in this case in the EHR space, is the development of CLEARPATH (*CLE*veland *A*rea *R*esearch *P*latform for *A*dvancing *T*ranslational *H*ealthcare). Analysis of EHR data and data across multiple ongoing studies holds tremendous promise for clinical and translational research but faces challenges in extracting and harmonizing research relevant data, particularly by the use of disparate EHR systems across institutions. An additional complication is the unintended duplication of data, as the same individual may be seen (and have data generated) at the multiple institutions in multiple studies. To address these multi-layered problems, CTSC participating institutions are supporting the ICB's development of a research data warehouse that captures data from CTSC partners. CLEARPATH plans to have data feeds from affiliate hospitals through an Integrated Data Aggregation and Exchange System (IDEAS) appliance placed behind the affiliate's firewall to maintain security and privacy. CLEARPATH can hold a limited dataset (with the option for re-identification through IRB-approved processes) but uses a hash mechanism to provide a unique common identifier for each participant that allows tracking and integrating individual level data across the systems for research studies. Because the IDEAS appliance rests behind the firewall, it is straightforward to provide data from any system data source e.g. captured through EHR, REDCap, Knowledge Program [collecting patient reported data], MyChart [an EHR patient portal], with IRB-approved consent process. The architectural design for CLEARPATH was completed in January 2016; testing of hashed ID process was completed in July 2016, and the database schema was finalized in October 2016. Testing of ETL processes is ongoing in 2017, and availability to the CTSC community for research use is planned in 2018.

CLEARPATH and SHED enable connections to external as well as internal data sources, some of them with very large files (e.g. raw MRI data, image files, genome-wide genomic data, data on physical environment relevant to health status, such as foreclosures, water shutoffs, lead in water from the NEOCANDO data base). Along with the ability to create a single integrated record per patient, integrating with additional data provides great flexibility in the questions that can be asked and the study designs used to answer them. This will be an important advantage for our researchers working together across our different sites in Cleveland.

Aim 1: Provide informatics tools and support to accelerate clinical and translational research.

One of the most difficult challenges in biomedical informatics is finding the interconnections and correlations among and across the variety of data in a manner useful for the translational scientist. The problems run the gamut from simple quality control checks (e.g. consistency of gender, height, and weight for an individual

across different clinical encounters) to providing structure to unstructured data (e.g. categorizing previous medical history and history of present illness) to overlaying geocoded data from social media. Increasing awareness of these universal challenges has enhanced the interest within the biomedical informatics community in finding solutions. We will adopt emerging best practices for use by the translational scientist.

We will continue to have a BIT consultant anchored at each site to provide the first point of contact for consults, queries, and basic training. This maximizes support across our three physical locations (CWRU/UH, CC, MH). The BIT leadership team will meet weekly with staff at their home institutions, and monthly in person or via web to review progress, set priorities, and address emerging issues and the Co-leads will report regularly to the Executive Committee. With BIT leadership guidance, BIT staff will develop and implement our coordinated data warehouse activities, and support investigator studies across the CTSC.

Data Integration is a significant challenge where success leads to new and important insights. We have substantial experience in integrating clinical data (whether abstracted from or pulled directly from the EHR) with genetic and genomic data, examining the genomic influences on one (Genome-Wide Association Study, GWAS) [(1)] or all (Phenome-wide Association Study, PheWAS) phenotypes[(2)]. This integration can be extended to include imaging, patient reported, behavioral, mHealth, economic, environmental, and governmental data. As one example of these additional data types, the CC has developed and deployed the Knowledge Program [KP] and MH has deployed MyChart, collectively enabling over 500,000 patients to contribute their own physiological and survey/self-reported data to our research endeavors. We will respond to data requests from CTSC investigators and components by identifying the necessary data sources, determining their structure, size, and availability, and developing an appropriate schema leveraging NLM's Common Data Elements (CDE). This promotes integration and facilitates interoperability with data from external sources.

Data Harmonization is required to successfully identify and use the same (or similar) measures that may have been captured and stored in different ways. This can vary from simply generating a data dictionary of variable synonyms to requiring changing data types (e.g. integer to real numbers) and multiple data transformations (e.g. regression or normalization of quantitative measures). We approach this problem by:

- The use of validated and standardized data capture forms, data dictionaries, and common data elements. Both REDCap and SHED have implemented standardized PhenX measures (see letter of support).
- The extensive use of validation checks in the EHR data to create consensus variables for static data recorded in multiple places (e.g. birthdate, sex, adult height, etc.).
- Application of statistical methods to adjust laboratory measures for consistency across labs.
- The use of natural language processing to structure unstructured data (e.g. cTAKES, TIES).
- The use of a de-identification encryption algorithm that creates a unique hashed ID allowing secure connection of individual level data across data sources without violating privacy.

We strive to provide a secure and flexible data environment and ensure that data types and sources are compatible with emerging national standards. Data harmonization tools include the National Human Genome Research Institute (NHGRI)-funded PhenX project, which provides over 500 harmonized measures across 24 domains (V 21.0) useful for both new data collection and post-collection harmonization activities.[(3)] EHR data can also be mapped to many of the National Library of Medicine's UMLS vocabularies including LOINC, a database of medical laboratory observations, MeSH, RxNorm, and SNOMED. We will employ HL7 international standards for data transfer between software. We will also start implementing methods for structuring unstructured data (e.g. free text)[(4)]. EHR data in CLEARPATH is mapped to the Observational Medical Outcomes Partnership (OMOP) common data model, which utilizes several different mapped ontologies and is being used by the eMERGE network and the "All of Us" initiative both funded by NIH.

Data Maintenance and Provenance is a critical aspect of any informatics infrastructure**.** The BIT will expand the infrastructure necessary to maintain data throughout its lifecycle and also provide tools for tracking data usage and provenance, a particular expertise of Dr. Sahoo.[(5)] We will provide overall data quality management by implementing a metadata-driven approach. For many studies, developing and implementing guidelines for generating data freezes (often representing the dataset used for a publication) is sufficient. For more complex studies (e.g. clinical trials), we will coordinate with *Regulatory Knowledge* to assure that all necessary data tracking and provenance is implemented. Many federal agencies and an increasing number of journals require deposition of data into a public repository (e.g. ClinicalTrials.gov, dbGaP) and the BIT will assist investigators in this process, working with *Regulatory Knowledge* and *Research Methods* teams, to provide processes and support for these important activities by *Hub Research Capacity, Network and Community*.

Study Design Consultation, Cohort Development and Analysis: Biomedical informatics consultants at each CTSC site will assist researchers with their study designs. They will leverage the available systems including the REDCap, SHED, CLEARPATH, eResearch and Explorys. An essential first step in clinical research, that often slows study progression, is the efficient recruitment of eligible participants to test hypotheses in clinical research. CC created the informatics support tool eResearch in 2000 to search EHR data in a HIPAA compliant manner to identify eligible patients based on computable inclusion and exclusion criteria. eResearch has been used for nearly all ambulatory studies since 2000 and inpatient clinical care since 2006 in the multi-specialty group practice at CC identifying participants who qualify for studies. The eResearch data base/search engine has substantially augmented and accelerated enrollment and diversity of participants without significant increase in costly screen failures at CC. eResearch services will be expanded beyond CC to include support of feasibility testing and study design at other CTSC institutions. Epic Slicer-Dicer tool at MH permit researchers to perform feasibility testing using de-identified EHR-derived data. Cohort identification will be enabled with appropriate Reliant IRB approval (with support of *Regulatory Knowledge*).

Extracting Phenotypes from EHR Data: Identifying cohorts or testing hypotheses using EHR data requires carefully defining the inclusion and exclusion criteria for participants (most often as cases or controls). Dr. Crawford has extensive experience in extracting and analyzing these data using natural language approaches.[6,7] For certain phenotypes standardized validated algorithms are available (the Phenotype KnowledgeBase; https://phekb.org)[REF:[8] which Dr. Haines helped develop. If no such algorithms are available, we will help investigators to develop and validate an appropriate algorithm. In some cases, this is straightforward (e.g. a combination of ICD and CPT codes), and in others it can be substantially more complicated (e.g. inclusion/exclusion of medications, temporal order of tests). Both Drs. Kaelber and Xu have designed studies taking advantage of these types of data.[9,10]

User-Friendly Access to the Data: Having extensive and connected datasets is of no value if the translational scientist cannot access them in a manner that promotes the asking and answering of relevant and important questions. After appropriate credentialing at one of the participating health systems, the user can easily and securely access multiple resources from their desktop. For example, the SHED has a point and click user interface (Qiagram) allowing access to the data from investigator initiated studies. Qiagram presents potential data sources, types, and variables. The user can then select the subset of data necessary for initial decision making (e.g. obtaining necessary sample sizes), set up data filters (e.g. only males over age 50 with type II diabetes), and extract data for analysis (after appropriate review and approvals).

Subject Identification, Recruitment, and Engagement: Identification of study participants at the point of care affords the best opportunity to engage patients for studies. EHR tools and alerts will help identify potential participants to enhance enrollment and ongoing engagement as they access the care continuum. Mobile enabled tools such as MyChart allows for delivery of questionnaires and collection of participant generated data from questionnaires and wearable devices. Knowledge Program (KP) provides a scalable platform to systematically collect patient-reported data through a mobile ready web-based data collection system. The system is independent of but tightly integrated with the CC's Epic EHR through HL7 and web services feeds. We will leverage and expand our outreach to the community using social media in coordination with *Hub Research Capacity* and *Network Capacity* components to further engage and educate the community at large.

Development of New Tools: We will provide multiple development environments for developing and testing new biomedical informatics tools, leveraging additional resources (e.g. through the ICB) as necessary. Such tools might include:

- Standardizing and storing (often complex) queries to access stored data, particularly from the EHR
- Natural language processing for generating structured data from unstructured data such as free text
- Application Program Interfaces (API) to collect mHealth data from wearable and mobile devices
- APIs to access and process federated data within and external to the CTSC
- Statistical methods to identify and correct erroneous data
- Computational methods to impute missing data
- Methods to provide visualization of complex data and results

Data Security: Each hospital system already has privacy and security offices that maintain a high level of data protection for their patient-oriented data. Similarly, CWRU maintains state-of-the-art approaches to data security. In light of the numerous data breaches reported in the public media and the ever changing and increasing security needs, we will designate a named security officer charged with assuring security and privacy compliance for the CTSC.[11] This extra measure of protection is necessary and appropriate to

minimize the risk of such breaches. Examples of the duties for this officer are making secured meta-analysis opportunities available for investigators[12] and applying methods to guard against attacks of the dataset in situations where third-party storage opportunities (such as Amazon Cloud services) are used.[13]. Overall, CWRU maintains a secure research environment (SRE) for computing, governed by a risk-based security program that includes controls that meet recommendations or requirements of regulatory and information security standards (including HIPAA, HITECH, FISMA, and SANS/ISO recommendations). The SRE is hosted in a HIPAA-compliant & professionally managed Tier III datacenter with physical and software security technologies, hardware/software failover redundancy, and daily backup routines with encrypted and redundant off-site storage (see letter of support). All systems in the SRE are actively monitored and maintained by dedicated and credentialed (security and technology) staff, and data transmissions inside and outside the datacenter are encrypted using SSL public key encryption, with file level encryption technologies utilized when appropriate. The SRE hosts both SHED and CLEARPATH. Similar controls are in place at all hospital systems to secure their EHR and PHI data.

Aim 2: Educate and train researchers, trainees, and staff in biomedical informatics tools and resources

Workforce development can take many different forms, from informal individual training to formal degree granting programs. The BIT will provide support and training for staff, trainees, and faculty.

Provide Basic Support and Training for Biomedical Informatics Tools: The BIT will engage with each project PI and component director to assemble study workflows, data dictionaries and custom data capture forms to ensure that administrative and research needs are met. Customized data management capabilities powered by multiple applications and interfaces provide: Lab-specific data entry parameters, enhanced basic or translational science data management, multi-institution / department / discipline common input screens and administrative program tracking tools. Online tutorials will be adopted from other resources (e.g. open source, other CTSCs) or developed to provide access at the convenience of the user. Informal training sessions for basic tools such as REDCap will be arranged for individual researchers. Given sufficient need, group sessions can be provided. If there is enough demand across the CTSC, we will implement video-conference sessions across the campuses.

Expand Formal Biomedical Research Informatics Education: Proper use of technology has become an increasing important enabler for successful translational research. Our goal is to offer a full range of formal and informal activities to meet the diverse biomedical informatics educational and training needs of the CTSC community. Formal training programs (at the certificate, masters, and doctoral level) anchored at MH and CWRU SOM are organized through the ICB's Center for Education and Training in Health Informatics. Development of and access to all programs will be closely coordinated with the *Translational Endeavors, KL2,* and *T1* components and monitored by the TWD Advisory Board. CWRU also has an ACGME accredited Clinical Informatics Fellowship program, based at MH. Informal training via presentations, seminars, and communication media will provide elevated awareness informatics principles to the CTSC community at large.

Studios: A major hurdle to appropriate implementation of biomedical informatics approaches is simply a lack of knowledge for the biomedical informatics naïve researcher. To reduce this hurdle, the BIT will implement a monthly "studio." The format of the studio will vary depending on the needs of the research community. For example, we may provide tutorials on the use of existing biomedical informatics tools (as mentioned above), including the processes and requirements necessary to access and deploy them. We may provide tutorials on the biomedical informatics needs of a proper study design, including good laboratory practices as they relate to biomedical informatics, emphasizing the need for security, privacy, and data quality and provenance. We will also provide the opportunity for individual researchers to bring their question/problem/study to a panel of experts to review and suggest possible solutions. Particularly in this latter case, the involvement of other components such as *Research Methods* will be essential to provide overall guidance.

Aim 3: Enable collaborative research within and outside the CTSC

The BIT is actively involved in multiple national and international biomedical and medical informatics efforts (e.g. NIH's BD2K, multi-institutional PCORI grants, CDC Diabetes Cohort project, the American Academy of Pediatrics CER^2 network). Along with active participation in the CTSA informatics DTF, these activities provide multiple points of contact that assure optimal data integration and harmonization activities promoting interoperability internally and externally.

Integration/Coordination with Other CTSAs: Collaboration with the broader research community will be facilitated through multiple channels. For individual research studies, the BIT will facilitate data transfer using

secure protocols (e.g. secure FTP with temporary password access) after documenting that the necessary data use agreements are in place. In other situations, federated data access may be preferred or necessary. We are implementing I2B2 and SHRINE as one such federated approach; we will work with the outside researchers to identify an appropriate solution if I2B2/SHRINE is not appropriate. For example, we have engaged with TriNetX, already deployed in 24 CTSA hubs. Biomedical informatics tools we develop will be shared as broadly as possible, usually though free open source licensing. However, in some cases real value for a the tool may only be realized with substantial effort and capital, best obtained through commercialization.

National Recognition, Interactions and Collaborations:, We will encourage participation in national networks and consortia, assist the *Administrative Core* in identifying and disseminating opportunities, and provide the necessary biomedical informatics support for participation in such activities. Our informatics faculty and organizations are already national leaders. Dr. Kaelber directs an ACGME approved Clinical Informatics fellowship and heads a team of over 30 physician and nurse informaticians at MH, which was recently recognized with Health Information Management and Systems Society (HIMSS) enterprise Davies award for its use of health IT and is in the top 1% of all healthcare systems in the country for its use of health IT. Dr. Kaelber is also the incoming Chair of the Epic Corporation's COSMOS Data Research Governance Council and Dr. Louis Capponi from the CC is an incoming Council member.

Engaging the Community: The BIT will work closely with the *Community and Collaboration* component to identify opportunities and support multiple different modes of engaging the community in translational research efforts. Examples include:

- Patient Oriented Data Entry: As described above, the KP platform enables collection of patient-reported data through a mobile ready web-based data collection system. Similarly, MH has employed the MyChart patient portal to acquire patient-centered data. We will expand the use of Blue Button and other external data sharing applications, already enabled at MH and CC, so that participants who received care outside the current CTSC health systems can provide their EHR data for research.
- Data Capture From Mobile Devices: Mobile device monitors are being piloted in patients with heart failure (at CC) and obesity (at MH). Apps have also been developed to capture usage of farmer's markets based on incentives, particularly in areas in or near food deserts.

Enhance Research Networking: Promoting collaboration both locally and nationally is a priority of the BIT. Two examples are Pure Experts, which catalyzes collaboration by providing research-related information on CTSC investigators and the ability to perform aggregate searches across the multiple studies housed within the SHED. These tools assist researchers to (1) Identify investigators focused on similar work; (2) Assemble multidisciplinary teams to pursue translational and collaborative research; (3) Find a mentor; and (4) Provide awareness of new faculty and other researchers working in a related science area.

Support CTSC Component Assessment: The BIT will assist each component of the CTSC to develop, collect, and report metrics that assess their success. For example, for the *Hub Research Capacity* component our staff will work to implement a data feed for data already collected by the institutional research offices for new projects and help implement a simple data collection form for data necessary for the metrics.

EVALUATION METRICS: INFORMATICS		
Aim	**Frequency & Method of Assessment**	**Evidence of Success (Metrics)**
Aim 1: Provide informatics tools to support and accelerate clinical and translational research	Quarterly review of BIT and ICB activities, Pure Experts; Semi-annual BIT reports to CTSC leadership	Process: increased # of studies supported, data sources integrated and harmonized. Increased # of cohort development projects, variety and usage of biomedical informatics tools. Increased # clinical research subjects. Outcome: # publications, patents
Aim 2: Educate and train researchers, trainees, and staff in biomedical informatics tools and resources	Semi-annual BIT reports to CTSC leadership; Registrar reports.	Process: # enrollees in formal biomedical informatics coursework, fellows enrolled, studios held and attendance. Increased # biomedical informatics consults performed. Outcome: degrees awarded, jobs obtained.
Aim 3: Enable collaborative research within and outside the CTSC	Semi-annual BIT reports to CTSC leadership; Registrar reports.	Process: # projects using standardized tools, collaborative projects, # datasets shared, amount of data shared locally and nationally Outcome: # collaborative projects and publications.

C. Community and Collaboration (C&C)

SPECIFIC AIMS

The goal of the CTSC *Community and Collaboration (C&C)* component is foster effective investigative teams enriched with our diversity of stakeholder communities, to address, together, the health and health care priorities of our population.

The greater Cleveland community has both tremendous need and unprecedented opportunity to translate research findings from our lab, clinic and community studies into interventions that can be implemented and tested in collaboration with a broad range of partners to improve the health of the population and reduce inequalities. Members of our CTSC Shared Resources for Community Engagement and for Practice-Based, Population Health & Outcomes Research have been developing strong working relationships with diverse clinical and community stakeholders for more than two decades. Our Translational Technologies Resources Core has developed an extensive network of industry and philanthropic partners to develop new technologies and facilities that enable clinical and translational research. This has resulted in a vital foundation of research and development collaborations across five distinct but overlapping communities (Figure 1).

Figure 1: Our Communities of Collaboration

As part of a highly participatory ongoing collaborative with our **public health and community partners,** we have co-developed a countywide health improvement plan (Health Improvement Partnership – HIP-Cuyahoga) that uses a collective impact approach and a health equity lens to implement a strategic plan prioritized by local residents.[1] It provides a clear, actionable role for the CTSC. From this collective plan and partnership has come collaborative intervention development, implementation and dissemination. An example is a $7M NHBLI-funded multi-level obesity treatment trial conducted in partnership with the Cleveland Metropolitan School District and the YMCA of Greater Cleveland that tests evidence-based practices with overweight/obese low income and minority adolescents and their families.[2] With our practice-based research networks of **community-based clinical partners**, we have developed novel interventions grounded in the wisdom of community discoveries that spawned dozens of community and health care system trials focused on improving evidence-based prevention,[3-19] one of which is now embedded into the structure of our pediatric Medicaid Accountable Care Organization.[4] With our **industry and philanthropic partners,** we have leveraged CTSC support to develop the NHLBI-funded National Center for Accelerated Innovations, which sources, evaluates, and develops technologies from across all Ohio CTSAs and gathers knowledge about best practices, along with specific business intelligence around our discoveries. With our **grassroots and patient advocacy partners**, particularly our highly engaged community advisory boards, we have developed a deep and wide-reaching network of individuals and groups that are committed to work with the CTSC to advance the awareness, understanding, and need for research to improve the health of all citizens.[7, 20-22] While significant progress has been made, there is still much work to be done to fully optimize the connections of these communities with our **trained investigator teams** (the fifth "community"), forming the transdisciplinary teams needed to "turn observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public" (*from the FOA).* To expand, strengthen and intensify our diverse partnerships locally, regionally, and nationally to deepen skill, experience and transportable knowledge in team science, and help to further institutionalize community collaboration/team science as a normative approach to research, we propose the following **specific aims:**

Aim 1: Create and foster opportunities for cross-disciplinary investigators and their aligned stakeholders to collaboratively produce novel and relevant translational research.

Aim 2: Build capacity of our community and clinical partners through training and resources to be strong and equitable research collaborators.

Aim 3: Build capacity among faculty, trainees, workforce and diverse community partners to engage and promote team science.

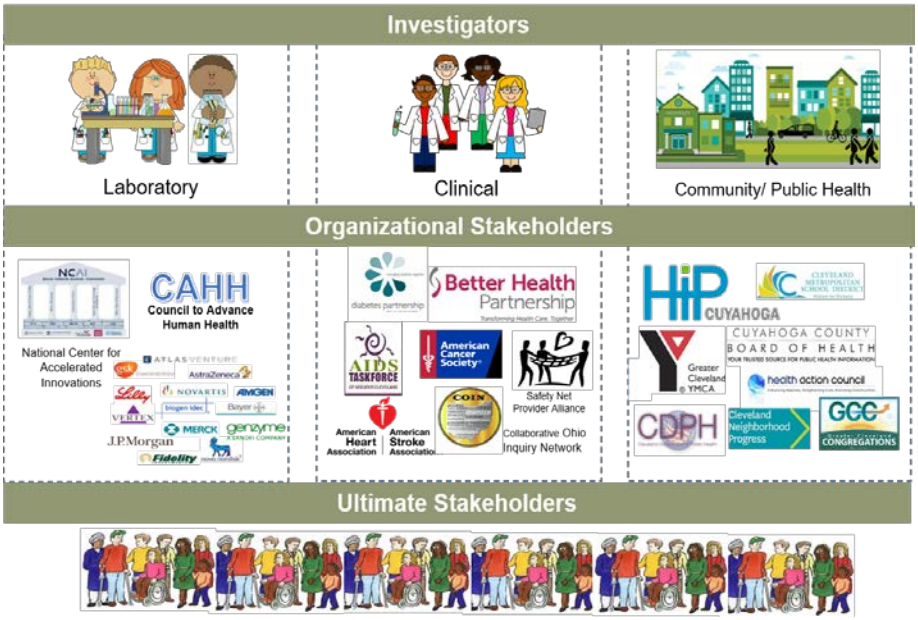
Aim 4: Facilitate institutional policy and environmental changes that encourage, motivate and integrate team science and stakeholder engagement in a culture of inquiry.

Component Lead: This component will be led by **Elaine Borawski, PhD**, Professor of Population & Quantitative Health Sciences and Nutrition and the Director of the CWRU Prevention Research Center.

Community and Collaboration (C&C)

Goal: Using a well-defined and performance-based implementation plan, we seek to further develop and foster effective investigative teams that can work together with a diversity of stakeholder communities, to address the significant health and health care priorities that face our society.

Over the past decade we have worked diligently to help our laboratory, clinical and community investigators to develop and foster meaningful, equitable and productive stakeholder relationships – with individuals, groups and organizations that have a stake in the outcome and whose input could greatly enhance the research endeavor. The figure to the right provides a visual of these efforts. Each investigative group typically has its own set of stakeholders; however, the ultimate stakeholders are the residents of our community. It is their health and the disparities that they experience that drive these relationships and the collective work that comes from them.



As an example, with our public health and community partners we **co-founded HIP-Cuyahoga (HIP-C)**, a county-wide collective of over 100 entities and nearly 600 stakeholders and community partners (www.hipcuyahoga.org). This consortium was formed to address the significant health disparities documented in the local community, such as a **24.5 year difference in life expectancy in two communities just 8 miles apart**.[23] A community health assessment (co-led by Elaine Borawski) documented minority and low-income residents suffer disproportionately from chronic disease and health risk behaviors associated with disease development and progression (e.g., obesity, smoking).[24] In addition, over 7,000 community residents completed their own assessment of the most significant health issues and priorities (also spearheaded by CWRU faculty). This resulted in an equity-focused community health improvement plan[1], vetted by stakeholders and residents, prioritizing four strategic areas, each with detailed action plans and measureable outcomes. Not only does the health improvement plan provide guidance on what is important to the local community, **each strategic area has significant opportunity to conduct collaborative and transformative research,** greatly benefiting from the expertise and resources of the CTSC, with initial evidence in hand. Since 2013, this alliance has leveraged over $13 million in funding to implement evidence-based interventions within the Plan, including a $6 million grant co-written by CTSA faculty and HIP-C partners, targeting obesity, hypertension and diabetes prevention and management though improved clinical care. HIP-C provides us with a community "laboratory" to test new approaches and interventions; however, not by simply "dropping in" an intervention but having it evolve from the partnership itself, an approach that is far more likely to be effective and sustainable.[25,26]

We have similar success stories in our clinical and laboratory collaboratives (described in the next section).The lessons learned greatly inform our plan going forward. We've learned that collaboratives emerge organically and through intentional direction and support. That both investigators and stakeholders need training on how team based research works (and works best) and an awareness of how the "other" approaches problems, views progress and success. And that these diverse teams are the most likely to flourish and succeed if the culture values, supports, and incentivizes the collective work. Our plan is built upon these lessons and implemented through the four specific aims of the *C&C* component.

Leadership: The *C&C* is led by **Elaine Borawski, PhD**, Professor of Population & Quantitative Health Sciences and Director of the CWRU Prevention Research Center for Healthy Neighborhoods. The leadership team also includes **Kurt Stange, MD, PhD**, Professor of Family Medicine and Community Health and **Mark Chance, PhD,** Professor of General Medical Science and Vice Dean for Research for CWRU School of Medicine. The composition of this team is intentional - each of these individuals has a highly successful track record of leading collaborative teams in translational endeavors within their own investigative area: basic science (Chance), clinical/PBRNs (Stange) and community/public health (Borawski) – and they work well together. This experience

and expertise is vital to the *C&C* as they will each facilitate the development and sustainability of investigator-to-stakeholder relationships within their respective realms, and finding ways for investigators across the continuum to explore new ways together to address the significant health issues and health disparities that face our nation.

C&C: Community Engagement

Aim 1: Create and foster opportunities for cross-disciplinary investigators and their aligned stakeholders to collaboratively produce novel and relevant translational research. As described above, we have worked intently to make connections between investigator groups (laboratory, clinical, community) and their most closely aligned stakeholders. This not only allows for collaborative teams to emerge, but also establishes trust, rapport and respect with stakeholders so that new clinical and community investigators may more easily connect to their study populations through these stakeholder connections and laboratory investigators can accelerate their studies through industry and foundation connections. We describe some of our most successful collaboratives:

- **Community Health Needs and Improvement (HIP-C):** HIP-C provides one of the most inclusive opportunities for researchers and community partners to engage, brainstorm, and work together to translate research findings into practice, and for practice-based evidence to inform new research. It brings together multiple academic and community partners in shared leadership. Each strategic priority area has formed a working subcommittee, providing an ongoing mechanism for making CTSC research relevant to community health. Currently, well over a dozen CTSC faculty are actively engaged in the four subcommittees and CWRU serves as the "anchor institution" for two (healthy eating and active living; linking clinical care and public health). The CTSC will continue to support faculty serving in key leadership roles (Heidi Gullett, MD, Family Medicine, is Co-Chair of the Steering Committee, will support the next community health needs assessment (fall of 2017), and most importantly, continue to support the development of community-academic investigative teams within the consortium to conduct collaborative, translational research linked to the four strategic areas.
- **Health Care Data Sharing and Learning Collaboratives:** The CTSC will continue to support **Better Health Partnership** (www.betterhealthpartnership.org), a highly successful practice-based research network that works with over 170 pediatric and primary care practices across the region to improve health care delivery.[27] Through bi-annual Learning Collaboratives, they bring together well over 100 academic investigators, clinicians and community health partners each time to share data from across the participating practices with the intent to develop and test best practices across the network. They have been extremely successful in dramatically reducing racial disparities in health care delivery[27] and are now broadening their models of care to include social determinants of health. CTSC *Informatics* will work to link geographically identified public health data (e.g., housing violations, violent crime, healthy food retail) with electronic health records in the Cleveland Area Research Platform for Advancing Translational Healthcare (CLEARPATH), with the goals of identifying "hot spots" for clinical and public health interventions. This is yet another key "laboratory of the future" where diverse data are combined with learning forums that engage investigators, clinicians and clinical stakeholders to find new, innovative approaches to improving health care delivery and reduce disparities.
- **Regional & Statewide Practice-Based Research Networks (PBRNs):** Reaching beyond the local community, the highly collaborative regional PBRNs are a novel cross-Hub resource whose impact is magnified through the Collaborative Ohio Inquiry Network (COIN), which brings together the state's PBRNs and three CTSAs with support from an AHRQ P30 grant. These networks comprise 277 practices, 1967 primary care clinicians, and over 3.9 million patients, and provide mechanisms for cross-Hub research and development in CTSAs across the country. This has led to an ongoing CTSC-led PBR training initiative involving 22 CTSAs that led to an NCATS U01 application, an AHRQ R13 application funded on its first submission, and the creation of a statewide practice-based clinical trials infrastructure supported by the Ohio Clinical Trials Collaborative. This has built capacity for RCTs within COIN's PBRNs, and will be a significant resource to the newly established Trials Innovation Network.
- **Council to Advance Human Health (CAHH):** To accelerate the development of technologies towards clinical testing, the CTSC helped to establish drug, device, and medical technology development programs to bridge the gaps, both in funding and in culture, to translating results from basic science discovery to first in human studies. The CAHH (focused on drug development) and the Case-Coulter program (for device and medical technology development) have received partial support for project managers and industry consultants (see Budget Justification) to mentor faculty one-on-one to plan projects and build appropriate project teams for acceleration of specific technologies. This has led to licensing of 17 technologies to industry and 18 programs achieving first in human testing, resulting in follow on funding of $65M either directly to investigator laboratories (~$15M) or to university spin-outs (~$50M) from foundations, venture funds, and industry. We will continue to identify and accelerate promising technologies via team building and stakeholder (sponsor) identification.
- **National Center for Accelerated Innovations (NCAI):** The value of CTSC support and leverage is evidenced

by platform expansion in 2013, when our CWRU-led Ohio CTSA consortium was awarded an NHLBI-funded Center for Accelerated Innovations grant, which sources, evaluates, and develops technologies in the heart, blood, lung, sleep domains. This has led to the evaluation of 217 technologies and granting 27 awards of ~$150K each. The NCAI is composed of the Ohio consortium and two other consortia, the Boston Biomedical Innovation Center and the University of California Biomedical Research Acceleration, Integration and Development Center. Through national joint meetings we evaluate and share best practices in product development funding, management, training and entrepreneurship. The collaboration also led to a partnership with the Harvard CATALYST program to share ideas about best practices across CTSAs and brainstorm new pilot initiatives (see *Translational Endeavors*). Many lessons have been learned from these and other examples, the most important being that success comes from having diverse research teams that communicate and collaborate effectively. The CTSC support provides a backbone and vision for the program that continues to cement its sustainability and momentum going forward.

- **Support Community Advisory Boards (CABs) as Vehicles for Translational Research:** Our CTSC relies on a number of advisory boards to provide invaluable guidance, support and reality checking with regard to how well our work connects to the local community. Our Prevention Research Center, Center for Reducing Health Disparities and Case Comprehensive Cancer Center each have highly engaged, grassroots advisory boards that reach deep into the community. The Practice-Based Research Networks, including Better Health Partnership have strong advisory boards of community-based clinicians, patients and public health officials. The Council to Advance Human Health has councils of industrial advisors to assess business opportunities, refine project plans and assist with project engagement. Increasingly, **these groups are seeking larger scale impact.** For example, the three Ohio CTSA CABs came together to support a cross-Hub Precision Medicine Initiative application, offering strategies for communication, recruitment and retention. We plan to capitalize on these interests by empowering them to explore initiatives they'd like to champion, locally and across the state and nation and for them to work more closely with the Integrating Special Populations (ISP) team of *Hub Research Capacity (HRC)*, assisting with making community connections and help recruit residents for focus groups/interviews.

Our plan is to work closely with these **established collaboratives** to support new investigative teams to **develop and test novel and innovative interventions, technologies and best practices together.** With each group we will develop an individualized action plan, provide administrative assistance with planning meetings and grant preparation; help to identify new grant opportunities, provide stakeholders with support and training to be effective grant collaborators (see Aim 2), provide pilot grant opportunities, and assistance with dissemination of findings. Progress reports and performance milestones (# grants, new technologies, manuscripts, and toolkits) will be required of these groups. In addition to working with these existing collaboratives, the *C&C* team will also support **three other approaches to investigative team development:**

- **Emerging collaboratives**. For relationships between investigators and stakeholders that have not yet yielded collaborative work, the *C&C* team will provide short term, adminstrative support to convene meetings and retreats (scheduling, finding space, notetaking), help to gather information on current research and interests of potential members, and develop a collective plan. If successful, we would ask that members participate in a team science workshop (see Aim 3), which would then provide them access to the resources outlined above for the more established groups. An example is a group of basic science, clinical and public health investigators, along with clinic and community stakeholders who have recently connected through the Case Comprehensive Cancer Center, all interested in working collaboratively to reduce tobacco use and its health impact in the city of Cleveland (current use is ~40% compared to 20% nationally). Because of the breadth of membership, they have great potential of being a powerful, productive and impactful collaborative; but would benefit greatly from the resources and support that the *C&C* could give them, including team development resources and pilot funding.
- **Investigator(s) or investigative teams that have not yet linked to a stakeholder**. We believe this is what the C&C component does best. We have developed a very large network of industry, clinical and community stakeholders who share in our mission to improve health and reduce disparities. We expect that this component will be the most aligned with *HRC*, who assists investigators conducting clinical studies to connect with potential participant populations. We will draw upon our collective resources and connections to help link investigators to relevant stakeholder groups that can provide insights into the problem, help to develop successful recruitment strategies and assist with interpreting and disseminating the findings.
- **Stakeholders** interested in collaborating with CTSC investigators. As awareness of our CTSC grew over the past decade, so have inquiries from potential stakeholders interested in collaborating with investigators on issues and topics important to them or their constituencies. Many are now linked to one of the established collaboratives; however, we are well prepared to work with the new stakeholders. For community organizations

or clinical partners, we may first guide them to our training programs (See Aim 2). For others we may set up introductory meetings with investigators or guide them into one of the established collectives.

Linking to Hub Research Capacity and Network Capacity. For studies emerging from collaboratives that involve human subjects recruited from one of the hospital systems or their community clinics, the *C&C* will help link these investigators to the *HRC* team, who can help them determine where and how they might best recruit study subjects, develop the data collection protocols, assist with IRB, and help with recruitment, especially if the population is hard-to-reach. On the flip side, our *C&C* team will also serve as a resource to *HRC*, particularly the **Participant Recruitment Specialists** within each of the institutions, helping to link investigators to stakeholder groups that can assist with recruitment efforts. Also, as noted in the *HRC* component, the co-director of our Community Engagement Core from our last cycle, Dr. Ashwini Sehgal, will now work more directly with *HRC*, an intentional placement to help bridge the two components more effectively. As he works with the Participant Recruitment Specialists and the **Special Population Point Persons** in identifying best ways to integrate special populations, he brings with him connections to a broad networks of health-related community organizations, as well as a natural, well-established link to the *C&C* team.

Aim 2: Build capacity of our community and clinical partners through training and resources to be strong and equitable research collaborators. The translation of scientific findings into community and clinical settings needs strong, equitable and engaged collaborators who understand and value research, and the unique and powerful role they can play within the research enterprise. We will use our successful engagement and training methods to expand and deepen the capacity of our clinic and community-based partners through 1) training in research methods and team science, 2) support for team grant writing, and 3) access to online library resources.

1. Training: One of our most successful avenues for developing bi-directional community research partnerships has been through our innovative training programs aimed at increasing research capacity within local community and clinical organizations. **Partners in Education, Evaluation and Research (PEER)** was co-developed with nearly a dozen community organizations, providing a 14-month program that brings together a research fellow, organizational mentor (to help the fellow bring back what they learn to the organization) and a faculty member with a shared interest. PEER involves both didactic and interactive training, and culminates with a partnered research project conducted by the triad. We have graduated three PEER cohorts (n=16), which have yielded two dozen presentations, 2 manuscripts and 3 funded grant applications, with the structure and evaluation of the program published [28,29] Our PEER graduates have come from a wide range of organizations, many of whom are linked to one of the collaboratives described above. For many alumni, PEER is evidence that CWRU is truly committed to community engagement and community collaboration because we are using our resources to train and support *them* to better serve their own constituencies.

PEER Alumni (since 2012)

- AIDS Task Force of Greater Cleveland
- Care Alliance (FQHC)
- Center for Cognition and Recovery
- Cleveland Dept of Public Health
- Cleveland Rape Crisis Center
- Cleveland Regional Perinatal Network
- Cuyahoga County Board of Health
- Cuyahoga Co. Planning Commission
- Educational Services Center
- Environmental Health Watch
- Gathering Place
- Hunger Network of Greater Cleveland
- Komen Foundation of Northeast Ohio
- Neighborhood Family Practice (FQHC)
- NEO Healthy Fathering Collaborative
- OSU Extension - Cuyahoga

Going forward, we plan to engage 14 new organizations (or additional fellows from the same organizations to increase depth), drawing from our waiting list and intentional outreach. However, we also wish to deepen the skills and capacity of the organizations already trained. To do this, we will offer a select number of PEER graduates up to 15 credit hours of tuition to complete one of two certificate programs: one in clinical investigation and the second in quantitative research methods, each involving five, 3-credit courses. Based on expressed interest, we anticipate supporting four to five graduates over the course of the 5-year cycle. We will also continue to support to Fellows and encourage them to participate in other **team science and workforce development opportunities** provided by our CTSC. Lastly, planning is currently underway with five other CTSAs who have similar training programs to submit a cross-Hub application to co-develop a toolkit of shared curricula, alternative format delivery, online resources and evaluation tools with CTSAs across the country.

Our second training program is the **Certificate Program in Practice-Based Research Methods (PBRM-Cert)**. A product of the collaboration of 8 AHRQ-funded PBRN Centers of Excellence in Practice-Based Research and Learning, it seeks to develop a new generation of independent investigators within the PBRN community.[30] The program provides training in concepts, skills, and methods for conducting PBR and building PBRNs using four learning modalities: webinars taught by PBRN experts; local mentoring by an experienced PBRN investigator; development and presentation of a research concept paper for a PBRN study; and development and presentation of a refined Specific Aims section. The lean and highly scalable 10-month program is web-based with a national scope, but is also being used locally by clinician-members of the Better Health Partnership PBRN.

Endorsed by the North American Primary Care Research Group and supported by an AHRQ R13 grant, PBRM-Cert's first cohort contained 17 trainees and 20+ mentors from across the U.S., and its current second cohort comprises 54 trainees and 47 mentors. Of the 71 total trainees, 46 are from 22 different CTSA institutions. An NCATS U01 application was submitted in March 2017 to propose a program that builds on the proven methods of the PBRM-Cert. Led by the CTSC, the proposal is a collaboration of 6 CTSA hubs. The proposed program will made available to 62 CTSAs as a training mechanism and PBRN infrastructure-development resource.

2. Support for Team Grant Writing: Since 2009, our CTSC faculty have submitted over two dozen research-based grant applications with a community partner as key personnel, involving **40 unique partners to date.** This has often required significant time and effort on the part of investigators to help make their community partners "research ready". To consolidate this effort, we will create a **Grant Prep Support Team** that provides community stakeholders help with: developing their biosketches, becoming CREC certified, ensuring that organizations are able to apply and receive grant funding (i.e., compliance), and provide support for navigating grants.gov and eRA Commons. These services will be offered at the time of grant preparation, but the team will also be proactive, reaching out to investigators and community collaborators who might benefit from the service.

3. Provide Community Collaborators with Access to Online Library Resources: One of the most valued aspects of our community training programs, especially PEER, is the free access to the university's online reference materials, such as research articles, systematic reviews and evaluation tools. In the past year, we have established a mechanism for community organizations to apply for annual access to the CWRU library resources and to track usage. Going forward, we will provide access to up to 50 community partners each year who are: (1) research collaborators; (2) co-authors; or (3) participants in a training program.

C&C: Collaboration and Multi-Disciplinary Team Science

Aim 3: Build capacity among faculty, trainees, workforce and diverse community collaborators to engage and promote team science. Well-functioning interdisciplinary research teams promote scientific discoveries, breakthroughs, and innovation. Diversity in teams also enhances creativity and leads to better decision-making and problem-solving. The ability to function effectively in diverse teams, however, cannot be left to chance; the creation and fostering of effective diverse research teams involves **systematic educational programming and ongoing assessment.** Our planned activities build on a successful Interdisciplinary Team Science course and approach designed for our KL2 scholars that has been offered for the past eight years with extremely positive outcomes (new grants with collaborators across multiple disciplines and stages of translation, use of the Co-PI mechanism, high satisfaction of participants).The participants achieve competencies related to research group formation and leadership, trust building, group decision-making techniques, conflict management, creative thinking, giving and receiving feedback, and meeting skills. Having found these skills to be best learned in **interactive, experiential small group workshops** of participants from diverse disciplines, we will disseminate our best practices by extending them to our TL1 training program and offering them to mentors and advisors of our other K and T32 programs. We will also integrate these competencies for interdisciplinary teamwork in research into a range of activities across the CTSC to build team science capacity more broadly among faculty, trainees, research workforce, and our diverse community partners to support a culture of team science:

1. Offer small group training (multidisciplinary) seminars in Team Science at frequent intervals each year, offering at least one per year to one of the collaborative groups described in Aim 1.
2. Offer a 2-hr Team Building workshop for new research teams (e.g., pilots), or those experiencing challenges.
3. Inviting successful teams to share their processes and progress during a monthly Team Science Success Seminar series that will be held on a rotating basis across all the collaborating institutions of the CTSC.
4. Share best practices of Team Science course with directors and advisors of all T32 and K programs.
5. Highlight successful collaborations on the CTSC website, social media, getting the word out (see Aim 1)

Training Investigators on Stakeholder Engagement and Cultural Competency. To improve the quality of the interactions between investigators and culturally and linguistically diverse populations, we will continue to train local investigators on cultural competency in research. Using a guide titled **"Reshaping Research,"** developed by **Dr. Ashwini Sehgal** and his team, trainees may obtain up to eight CREC credits while learning to integrate cultural considerations into the research process (developing research questions, study design, data collection, analysis, and dissemination of findings). More than 250 researchers associated with CWRU, including affiliated hospital staff, trainees, and community-based investigators have participated to date. Please note that both the *C&C* and *HRC* will be advertising and promoting Dr. Sehgal's cultural competency training.

Aim 4: Facilitate institutional policy and environmental changes that encourage, motivate and integrate team science and stakeholder engagement in our culture of inquiry. Multiple forces, including the increasing complexity of science, advancements in our understanding of human interactions, and the increasingly

competitive landscape of the clinical and translational research environment, have opened the door for alternative models of academic success and best practices that in particular, reward team science via aligning the academic reward system with team science goals. CWRU, the faculty home for the CTSC researchers across Cleveland, has implemented policies intended to **encourage and value team approaches to research using the promotion and tenure (P&T) process (see letter from P&T Co-Chairs)**. Starting in 2006, the School of Medicine changed its bylaws to explicitly recognize team science as a pathway to promotion and tenure. From 2008-9 through 2015-16, 119 applicants for promotion (tenure and non-tenure track) identified themselves as team scientists: 115 (96%) were promoted. For the award of tenure, 44 of 49 (90%) of team science based applicants received tenure. Over the last two years, 17 promotions or awards of tenure have been based in whole (7) or in part (10) on team science. The CWRU School of Engineering, School of Nursing, and School of Applied Social Sciences now also credit team science in the promotion process (please see letters from respective Deans). In addition, our KL2 and TL1 programs provide explicit instruction in team building and maintenance. We are in the process of enhancing **documentation of collaboration, including stakeholder engagement scholarship** by adding a new reporting tab to the annual online faculty review form that all SOM faculty are required to complete in order to have their annual contract renewed. Beginning in 2017, faculty will report on team scientist collaborations, as well as grants and scholarships that include stakeholders. To describe and disseminate the SOM process, we have developed a Faculty Toolkit series, with sessions that explicitly lay out the case for team science in P&T. These sessions are videotaped and available to the CWRU community. In the future we will invite All CWRU faculty to these sessions. Lastly, we will promulgate team science best practices and, in concert with *Translational Endeavors* and the OTWD, disseminate these educational opportunities to the workforce across the CTSC institutions.

Showcasing Collaborative Teams and their Work. In addition to these specific institutional policies, we will help support the culture of team science and stakeholder engagement by showcasing and promoting successful collaborative work through: (1) the CTSC newsletter; (2) regular seminars and grand rounds at each institution; marketing materials that highlight collaborative groups; (4) senior faculty with successful track records in team science research to participating in and leading team science workshops (see Aim 3); and (5) hosting an annual Team Science Leadership meeting, aimed at Research Deans, Department Chairs and Program Directors to discuss institutional resources for communication and data sharing, institutional policies regarding team science (promotion and tenure) and successful team processes.

EVALUATION METRICS: COMMUNITY AND COLLABORATION		
Overall Aim and Objective	**Overall Evidence of success (Metrics)**	
AIM: To identify and respond to public health needs by fostering growth and productivity of effective teams of diverse stakeholders **Objective**: Form interdisciplinary teams with strong stakeholder engagement that lead to new and innovative translational research	1. # of grants that include investigators from multiple disciplines/departments and a minimum of one community stakeholder as key personnel (co-investigator). 2. Proportion of research project/grants with community stakeholder as key personnel	3. # of adopted clinical protocols that are direct result of collaborative (with stakeholder input) research 4. # of different "communities" that participate in design and conduct of research (not just as participants)

COMMUNITY AND COLLABORATION – AIM SPECIFIC			
Aims	**Measurable Objectives**	**Implementation of strategies (Milestones)**	**Evidence of Success (Metrics)**
Aim 1: Create opportunities for multiple disciplines and communities to collaboratively produce research	1. Leverage partnerships through existing collaboratives 2. Support development of new research working groups	• Engage collaboratives in C&C objectives • Provide support for: collaborative meetings; group goals/timelines; collaborative product development; pilot studies • Develop action plan for team development • Monitor progress reports & milestones	• Action plan developed • # of new investigative teams • # collab. community grant proposals leveraged (pubs., grants, toolkits) • % meeting milestones • # completed pilot studies
Aim 2: Build capacity for community/clinical collaborations via training & resources	1. Expand & strengthen partner capacity to do research and contribute to collaborative investigative teams	• Training in research methods & team science • Support for team grant writing • Access to online library resources	• # organizations trained • Products resulting from community-clinical team (paper, grants, protocols)
Aim 3: Build team science capacity among faculty, trainees, workforce and diverse community collaborators	1. Build new and strengthen existing investigative teams 2. Create & support team science success 3. Expand community involvement in team science	• Group team science training • Successful-team monthly seminars • Share best practices w/ T32 & K • Develop team training resources • Media highlights successful teams • Cultural competency training	• Academic-community teams that obtain grants • # teams that obtain training • # team projects in media reports ("ALT metrics")
Aim 4: Facilitate institutional policy & environmental changes that encourage all aspects of team science	1. Disseminate team science P&T policy across medical center 2. Increase faculty-community scholarship & collaboration	• Promote implementation of team science P&T policy across new schools • Faculty toolkit series on team science & evaluation • Track and evaluate stakeholder engaged scholarship	• P&T policies adopted & implemented by professional schools • # of team science faculty promoted or tenured. • # faculty who identify stakeholders as (a) co-authors; (b) co-investigators; or (c) research partners

D. Translational Endeavors (TE)

SPECIFIC AIMS

The CTSC provides an important hub for training investigators in the discipline of translational science. Complementing the workforce development effort, the CTSC also manages multiple pilot funding programs for establishing feasibility and validating initial hypotheses of early stage clinical and translational (C/T) research projects. During the coming five years, considerable training will be integrated with the 2019 opening of a new Health Education Campus (HEC). As the HEC will have an inter-professional educational vision and mission, its opening represents a unique opportunity to enhance clinical research training for the current and coming generation. The goals of the *Translational Endeavors (TE)* component are to: 1) enhance and integrate education and workforce development programs across schools of medicine, dental medicine, nursing, (biomedical) engineering, and our hospital affiliates and 2) extend and enhance the pilot funding program through streamlined review processes and funding of novel approaches that advance translation. .

Translational Workforce Development (TWD). Many of the workforce-related accomplishments noted in Table 1 reflect the influence of CTSC-initiated, CTSC-led, or CTSC-supported programs and the CTSC's vision to build a sustainable and innovative translational research enterprise. For example, 33 scholars have completed the KL2 program and over 75% have received external funding. We have launched new degree programs in clinical and translational research which are rapidly enrolling new students. We have helped PIs form translational research teams to accelerate biomedical product development. We have launched an NSF Innovation Corps (I-Corps) entrepreneurship program for drug development and a Venture Mentoring Service focused on biomedical innovation based on the MIT model.

Table 1: Workforce and Pilots by the numbers

Education Programs	
KL2 scholars (2005-present)	17 current 33 completed 26 independent funding
TL1 scholars (2007-present)	11 current 19 graduated 25 independent funding
Clinical and translational degree programs,	30 current
Workforce Development Training Programs	
I-Corps: NSF entrepreneurship training program (2015)	30 graduated
Faculty research teams developed and mentored (annually since 2012)	55 teams
CTSC Pilot Program	
Annual CTSC Pilots Awarded ($30K-$50K)	7/yr
Core Utilization Pilots Awarded ($5K-$10K)	30/yr

Pilot Translational and Clinical Studies Program (PTC). A major challenge to translational research remains the difficulty in securing funds for the validation of initial ideas and concepts while at the same time identifying the most promising, significant, and feasible projects in an efficient manner that productively allocate scarce resources. To assist with the latter challenge, we have established a web-based PTC review system with a 14-day review turnaround managed by an experienced and hands-on Pilot Studies review committee. This system and its CTSC leadership from CWRU and each affiliate hospital supports processes that provide timely feedback and mentoring to applicants while encouraging self-examination to promote continuous improvement. Overall, we will continue expanding the program to additional C/T pilot programs and adding features to CTSC funded projects to enhance timely project completion, including assignment of project managers to the programs.

Aim 1: Adapt the Office of TWD and its programs to be optimally responsive to workforce training needs:

- Expand and integrate the office to better connect programs within the CTSC community
- Link the workforce to available resources using novel tools including web-based content solutions and mobile devices
- Provide training in innovation, product development, and entrepreneurship

Aim 2: Advance translational science using pilot funding and a streamlined review process to spur development of novel methodologies, advance critical translational objectives for promising discoveries, including those related to health disparities and special populations.

Component Lead. This component will be led by **Mark Chance, PhD**, Vice Dean for Research and Graduate Education at the CWRU School of Medicine, Associate-PI of the CTSC, and Chair of the TWD Advisory Board. Dr. Chance is a Professor of Nutrition and of Genetics and Genome Sciences and is the holder of the Mathias Chair in Cancer Research. He is founder and director of the Center for Proteomics and Bioinformatics. Dr. Chance has over 280 publications and >12,000 citations of his work. Dr. Chance has led many peer-reviewed research programs, including R, P, U, and T-series grants from the National Institute of Health and peer-reviewed funding from NSF and USDA with continuous funding since 1990. He has also been invited to serve on many Government advisory panels and study sections.

TE: Translational Workforce Development (TWD)

Goal: The goals of the TWD sub-component are to: expand and further integrate the Office of Translational Workforce Development (TWD) across the biomedical workforce community and link the workforce to enhanced educational initiatives developed by the CTSC and partners (Aim 1a); enhance training initiatives in innovation, product development, and entrepreneurship, coordinate training initiatives across CTSC sites, and promote a C/T research diverse workforce (Aim 1b); and provide enhanced technology web and mobile solutions to enhance accessibility and immediacy of training (Aim 1c).

The Office of TWD was established to inventory, connect, and coordinate workforce training through the activities of the TWD Advisory Board, chaired by Dr. Chance (see *KL2* section). The board includes members from the *KL2* and *TL1* cores, educational leaders from the Schools of Medicine, Nursing, and Dental Medicine, and CTSC component leaders, and has functioned well to manage a diverse stakeholder group. The board, which meets one to two times per year and as needed, provides high-level oversight and advice on the balance of focus on the different objectives and outcomes assessment for the *TL1*, *KL2* and other TWD aims of the CTSC. This facilitates coordination and synergies between the *KL2* and *TL1* programs, and the TWD goals of this component. To expand our CTSC funded activities, we will hire a full-time Translational Workforce coordinator and add expertise in the form of educational consultants and programmers/web developers to the Office of TWD. The coordinator will integrate efforts to provide training and develop talent to enhance translation across Cleveland (letter from Blair Geho, CWRU SOM), and cooperate with partners regionally across Ohio (letter from Mark Low, NCAI-CC), nationally (letter from Cheryl Vaughan, B-BIC/Harvard CATALYST) and globally (letters from Yun Yen, Taipei Medical University, and Takeshi Tokuyama, Tohoku University). S/he will have an educational and clinical research background and/or experience and be a key administrative liaison to: 1) coordinate and evaluate relevant and necessary educational and training resources that currently exist in Cleveland and elsewhere, 2) initiate new education programs needed to complete the educational landscape, 3) help trainees understand gaps in their training, 4) monitor effectiveness of training, and 5) be an advocate for the career development aspirations and mentoring needs of a diverse workforce.

TWD Leadership: The TWD sub-component will be led by **Mark Chance, PhD**, and co-led by **Ofer Reizes, PhD**, director of Skills Development, I-Corps program at Cleveland Clinic. Support for the TWD will also come from program directors **Shirley Moore, PhD**, Associate Dean for Research, School of Nursing and associate director for *CTSTP/TL1*, CWRU; **James Spilsbury, PhD**, Head of the Center for Clinical Investigation's Academic Core and associate director for *CTSTP/TL1*, SOM, CWRU; **Ms. Carolyn Apperson**, CTSC Research Concierge; and **Paul MacDonald, PhD**, Associate Dean for Graduate Education, SOM, CWRU.

Aim 1a: Expand and integrate the Office of Translational Workforce Development (TWD) across the biomedical workforce community and link the workforce to enhanced educational initiatives developed by the CTSC and partners

The Cleveland translational workforce, outlined in Table 2, is a cohort of nearly 7000 physicians, scientists, engineers, students and research professionals with diverse background and wide-ranging needs for education and career development. Consistent with this, the existing infrastructure for research training (Figure 1) includes programs across a continuum from website postings (left hand side) to formal degree programs (on the right) across a range of disciplines important to C/T research, with most of these activities supported by CWRU and the affiliate institutions. However, as training opportunities are in some cases dispersed across the city, it is a challenge for trainees to individually mine for opportunities or in some cases to understand where there are gaps in their training. Thus, the CTSC staff and resources are critical for: identifying cross-institutional training needs, lowering barriers to accessing training opportunities, and providing oversight of the efforts, to maximize effectiveness and connectivity, while minimizing overlap and duplication, to support C/T workforce development.

Clinical research engages a wide spectrum of researchers having a range of qualifications and experience. By reducing training barriers, increasing opportunities for training, and identifying and encouraging underrepresented individuals we can enhance the quality of C/T

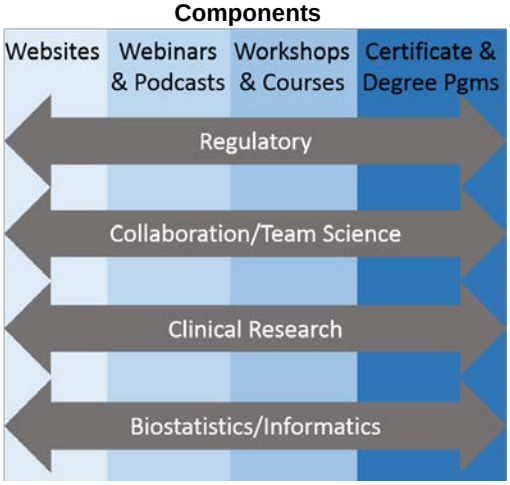
Table 2: Translational Research Trainees and Workforce

MDs and PhDs*	2814
Medical Students*#	888
PhD Students*	1020
MS Students*	798
PA program	60
Nursing Students	403
Dental Students	406
Research nurses, non-physician clinical workforce	493
Other research professionals (BS, MS)	657
Total	7539

*MDs and PhDs include CWRU faculty and post-graduate trainees at affiliate hospitals. Student data as of fall 2015. All medical, dental and nursing students and over 50% of MS and PhD students complete research projects in the clinical and translational space. Data includes undergraduates involved in research opportunities. # Includes 100 MD/PhD students

research. Thus, one-on-one mentoring, didactic group learning, and independent study guided by "smart" web resources will be identified, coordinated, and disseminated as part of the activities of this core. Figure 1 highlights the integration of our TWD efforts across CTSC components (e.g. *Informatics, Regulatory, Collaboration* and team science, clinical research and others). The Office of TWD will work with each of these components (supporting integration across components) and help flesh out the range of offerings from simple websites up to full degree programs across the range of educational opportunities. For example, Dr. Shirley Moore (TWD Co-lead) currently teaches a course in team science and the CTSC has organized workshops in this area. The Office of TWD will work with Dr. Moore to develop web and podcast content as well as workshops for team science. This will include unique content developed within our CTSC coupled to sourcing content from CTSC partners, such as Harvard CATALYST (see supporting letter). These approaches provide trainees with opportunities for exposure to team science concepts that have been vetted and benchmarked nationally through websites, podcasts, or workshops (despite potential barriers of time, distance, or cost). This approach will augment an infrastructure that can effectively coordinate CTSC education and training components (e.g. *KL2, TL1, Regulatory, Informatics*, and other CTSC components) with non-CTSC components (e.g. Graduate Education, Graduate Training Programs, Hospital credentialing programs, etc.).

Figure 1: TWD Integration across the CTSC Components



The goal is to make the Office of TWD a central administrative hub for CTSC-wide education and training that can interlink local and national resources, reduce barriers to a geographically and educationally diverse workforce, and provide content across a spectrum of C/T research topics. Below, we highlight programs that have had the largest impact and/or are especially innovative in promoting C/T research as well as approaches that are providing culture change at the CTSC institutions:

Graduate Degree Training. The Center for Clinical Investigation provides a comprehensive multidisciplinary clinical research training program with a PhD in Clinical Translational Science designed for individuals with an advanced clinical or masters' degree, a MS in Clinical Research for persons with advanced degrees or obtaining an MD, and a Graduate Certificate in Clinical Research for persons seeking foundational training in clinical research. PhD and MS programs are also offered in numerous other disciplines critical to advancing clinical and translational endeavors. The Office of TWD, guided by the TWD Advisory Committee, will provide integration of these programs by helping to develop websites, podcasts, and workshops to supplement didactic training opportunities to serve the non-degree C/T workforce trainees.

Good Clinical Practice and Clinical Research Certifications. Development of sound Good Clinical Practice (GCP) and Responsible Conduct of Research (RCR) guidelines is coordinated through a citywide CTSC-led Clinical Research Team Training Taskforce (CRTTT) headed by Dr. James Spilsbury (TWD Co-lead). Although each institution has individual responsibility to implement and monitor compliance with training activities, the CRTTT allows harmonization of training elements across the CTSC program and includes important partners (i.e., Cancer Center, Center for AIDS Research and other major clinical centers) in meetings to serve their needs and interests. **The CRTTT team has received a competitive supplement from the CTSA program (Fall 2014 thru September 2015) to streamline and standardize training in GCP across the entire CTSA consortium and has disseminated its findings nationally and is implementing them locally.** Additionally, partner institutions' Offices of Research Administration/Education conduct a wide range of educational activities (including a new clinical research boot-camp for research coordinators) for clinical research team members (investigators, coordinators, recruiters, data managers) involving training in electronic health records, regulatory and legal/institutional requirements, cultural competency, and unified IRB procedures. The taskforce is ideally suited to promote adoption of best practices for clinical trials across partner institutions, identify future areas that emerge as roadblocks, and advise the Office of TWD on most important initiatives needed to enhance C/T workforce training and effectiveness.

Research Credentialing at Hospital Partners. Concerns for participant privacy have prompted the use of specialized procedures to manage data when engaged in clinical research, creating barriers to collaboration across institutions. To ensure patient privacy and comply with regulations, our hospital affiliates have devised several options for maintaining up-to-date compliance with training in clinical research, and to allow researchers from different institutions to conduct research at partner institutions while maintaining all necessary safeguards.

The University Hospitals Cleveland Medical Center (UHCMC) credentialing program provides training for non-UHCMC personnel to access protected health information (PHI) and use internal technology systems so that they may conduct their research efficiently and successfully. UHCMC trained and issued credentials for over 600 non-UH personnel in 2016. In the project, the Office of TWD and the CRTTT committee will work with other affiliates to permit further expansion of cross-institution research.

Aim 1b: **Enhance training initiatives in innovation and entrepreneurship, coordinate training initiatives across CTSC sites, and promote a C/T diverse workforce**

Innovation & Entrepreneurship. A lack of adequate understanding of the requirements for commercialization and funding create major impediments to translation of bench research to the bedside. In support of CTSC efforts on innovation and education, the Office of TWD has partnered with the Cleveland Clinic to pilot an NSF I-Corps Hub for drug development (led by Dr. Reizes) in collaboration with the NIH National Center for Accelerated Innovations (NCAI) that includes CTSC partners across Cleveland and Ohio. Going forward we will use the I-Corps model to train investigators in the Lean Launchpad Business Model and coordinate with other skills development programs of the TWD office. Recently we have expanded our entrepreneur training with a CTSC guided program of venture mentoring (led by Dr. Chance) modeled on the MIT VMS model. In the current year we are piloting the mentoring of four ventures and intend to expand to supporting 10 entrepreneurs a year from both our funded translational research programs and KL2 scholars cohorts.

Outreach Regionally and Nationally. To expand the learning environment at the CTSC, the TWD supports collaboration at the state and national level, so that we can provide and receive valuable educational modules, avoid duplication of effort and disseminate best practices through collaboration, joint funding, workshops, training programs, and other educational experiences. Our partners in these ventures include The Ohio Consortium of CTSAs, which includes Ohio State University's CCTS and the University of Cincinnati's CCTST and the NCAI (see supporting letter), composed of the Ohio consortium and two other consortia, the Boston Biomedical Innovation Center (see supporting letter) and the University of California Biomedical Research Acceleration, Integration and Development Center. The NCAI programs, which fund drug and medical technology development, have held national joint meetings to evaluate and share best practices in product development funding, management, training and entrepreneurship. Going forward TWD staff will share curricula and best practices with our regional and national partners to enhance CTSC TWD programs.

Aim 1c: Provide enhanced technology web and mobile solutions to enhance accessibility and immediacy of training

Web and mobile resources for workforce development. A significant opportunity exists to provide integrated technology solutions using websites and mobile applications to market, disseminate, and evaluate workforce development and training initiatives and programs. Our goal is to create CTSC-wide mobile and web resources that connect educational initiatives and content with trainees ranging from the KL2 scholars to those needing simple, web-based certifications. We will create a unified portal (the TransTrain App) where scientists, students, and staff can: access educational resources, identify strengths and gaps in their knowledge, and document progress towards goals of interest. A key feature of the portal will be the ability for clinical researchers and support staff to create and share training plans and progress, including group formation, posting, push notifications, reminders and other advanced features of social network sites. Web/mobile-app templates can be shared across CTSAs. Planned features of the TransTrain App are an assessment tool that would allow researchers to understand their level of readiness for clinical and translational research in the context of their expressed needs for resources. Also, this tool would provide users with starting points for learning more by permitting seamless navigation to a carefully curated set of websites, podcasts, and YouTube videos. The Translational Workforce coordinator (and programmers) will develop, test, implement and support the TransTrain app with an initial pilot deployment to train in C/T research programs. S/he will continuously source updated content collaboratively with our NCAI and CTSC partners, and provide user support for the app to our CTSC members.

TE: Pilot Clinical and Translational Clinical Studies (PTC)

Goal: The overarching goals of the PTC are to evaluate, fund, and assess utility for proposals that advance translational science by: funding novel translational methods, such as proof-of-concept for new approaches, new technologies, drug/device development, and/or regulatory science advances (Aim 2a); funding translational research in areas of special interest, particularly in health disparities and special populations to leverage our strong *Community and Collaboration* component programs (Aim 2b); and promoting team building through collaboration between CT researchers and CTSC core facilities to encourage adoption of advanced technologies in C/T research (Aim 2c).

Limitations of funding to validate initial ideas is a major challenge for investigators, and pilot funding is key to address this challenge. The CTSC provides resources to assure efficient review, selection, management, and outcome monitoring of pilot programs. The CTSC has effectively used technology solutions to enhance pilot grants management since 2008. The WebGrants program has served as a backbone application for an entirely electronic grants management system, starting from initial upload of a letter of intent and/or application, to delivery of the notification letter. The popularity of the system has resulted in an expansion beyond its initial use in the CTSC to a role in assisting with review of other C/T research funding programs (Table 3). This technology is scalable, interactive across our CTSC institutions, and transportable to other CTSA programs. Beyond the technology backbone, the system connects a deep bench of reviewers through an administrative support structure guided by senior leaders from CWRU and all affiliates.

Table 3: Translational Pilot Applications Reviewed Using Webgrants

Program	Number of applications
CTSC Annual Pilots (2008-2016)	85
Core Utilization Pilots (2008-2016)	292
Non-CTSA Pilots* (2008-2016)	185

*Includes clinical and translational pilot grant programs from: Cystic Fibrosis Center, Skin Diseases Research Center, Taipei Medical University Pilots, NINDS SUDEP Center, Dept. of Pediatrics, Explorys, Comparative Effectiveness Research, Community Academic Partners Child

Key features of the implemented system include rapid turnaround (five to seven days' response for an LOI, 14-21 days for full proposals) using a wide ranging and established cohort of reviewers, support for delivering RFA information, uploading and sharing proposals and reviews supporting programmatic decision making on funding. There is no learning curve for use of this technology for application from submission and review, to outcome. Going forward, we will expand the use of Webgrants to help manage new pilot grant opportunities, such as the those provided by the Case Comprehensive Cancer Center, The Cleveland Center for Digestive Disease Pilots, and the National Center for Accelerated Innovation Pilot programs (see support letters), effectively doubling the number of LOIs and applications currently processed. Webgrants also will collate applications across applications and awards, permitting an accounting of faculty interests what the faculty regards as cutting edge research.

We constantly evaluate the pilot program for improvement and during the CTSC Retreat in 2014, the Pilot Program was specifically reviewed and discussed. Although the program was judged quite successful, it was recommended that going forward higher priority be given to funding for new methods to accelerate the C/T process and funding for pilot projects associated with our strong Community programs. To evaluate the first area of focus, we reformatted the 2016 Annual Pilot Program with an RFA call in Jan. 2016 with goals to conduct innovative translational research focused on the invention, preclinical development and/or first-in-man studies of novel therapeutic agents, biomedical devices, and diagnostics designed to address unmet clinical needs. We received 85 pre-proposals, selected 17 final proposals, and awarded three with start dates of June 2016. The quality and quantity of these first submissions is a promising start to the new approach. As investigators become more accustomed to the new guidelines and we further disseminate the results of this first competition, we expect submissions to increase rapidly. The next pilot round will evaluate pilot programs related to our community programs with an emphasis on research to examine health disparities.

PTC Leadership: The sub-component co-leads include the TE lead Dr. Chance; **Kingman Strohl, MD**, professor of medicine and director of the CWRU Center for Sleep Disorders Research at UH and VA; **John Sedor, MD,** professor of medicine and Vice President for Research at MetroHealth, and **John Kirwan, PhD**, professor of pathobiology and director of the Metabolic Translational Research Center at the Cleveland Clinic.

Aim 2a &b: Fund novel translational methods, e.g. proof-of-concept for new approaches, new technologies, drug/device development, and/or regulatory science advances. Fund translational research in areas of special need in the community, particularly health disparities.

Pilot Program Structure: The three major pilot programs listed in Table 4 will be the focus of the CTSC program, which will use the Webgrants infrastructure for proposal solicitation and review. Applications are accepted at specified times based on the particular RFA; with reviews for LOIs completed five days after proposals are received while reviews for full proposals are completed in 10-14 days. This timeline provides relevant scores and critiques to "sponsors" in a timely fashion promoting more rapid project initiation. Principal Investigator applicants must have a faculty appointment at CWRU, be on-staff at one of the CTSC hospital partners, and be eligible to submit an application to a larger source for federal or non-federal support. As successful pilots provide hypothesis validation they enhance competitiveness of follow-on investigator proposals for competitive peer reviewed funding. The Pilot program has a history of credibility and efficiency by operating in an evenhanded manner with fair, rapid, and helpful review, and with support for the investigator once the award is made, or gives feedback if it is not.

The CTSC Pilot Program Director (Ms. Kyriakides) serves as a point person for the PP process; often working closely with a point person from the relevant funder when the system is being used to review non-CTSC funded programs (see Table 3). This function is important for directing individuals in the community and from other CTSCs to appropriate expertise, programs or funding resources across the CTSC to build project teams towards a particular submission. The Pilot Program Steering Committee supports the Concierge in identifying individuals to build teams, focusing on credentials of applied and basic clinical research and/or experience in translational medicine.

Table 4: Proposed Pilot Programs of CTSC

Pilot Program 1	Pilot Program 2	Pilot Program 3
Novel translational methods	C/T research in areas of Community need such as health disparities or special populations.	Core technology and core facility collaboration
$30-50K	$30-50K	$10K
Funded by CTSC	Funded by CTSC	Funded by institutions
Bi-Yearly call and review	Bi-yearly call and review	Continuous call and monthly review
Pre-proposal Screening	Pre-proposal Screening	Direct submission
Accelerate faculty collaborations and translational science in feasibility and process in a novel area	Integrate across multiple disciplines to solve intractable problems responsive to high level CTSC goals	Test new technologies in the context of specific C/T research questions

Program Review Panels. The CTSA Pilot Grants Program has a two-step submission process comprised of short, pre-proposals followed by request for full proposals and expert review by the CTSA PTC Steering Committee, chaired by Drs. Chance (CWRU), Drs. Strohl (UH/VA), Sedor (MH), and Kirwan (CC) (Table 5). For each review, at least one member of the Steering Committee participates in the review. In addition, we will continue to recruit investigators from various Pilot Programs to serve on the Executive Committee for long-term advice and visioning of the program. Members serve in rotating three-year terms to provide continuity and consistency of evaluation, and progress reporting. Investigators on the Pilot review committees include Scientists, Clinicians, and Engineers along with ad hoc experts to cover the spectrum of Pilot applications.

Expectation Management and Applicant Support. The application process has two stages. In stage 1, a one-page pre-proposals describe the project's objectives, aims, anticipated outcomes, core disciplines and usage of CTSA resources and collaborating experts. The Pilot Grant Review Committee evaluates projects based on merit, innovation and the primary criteria prioritized (e.g. novel methodologies or areas of special need) along with consideration of secondary criteria (e.g., high translational potential, inter-disciplinary, >2 PI's from multiple disciplines, and/or inclusion of trainees) as laid out in the particular RFA. The review panel channels strong pre-proposals from stage 1 to full applications in stage 2 while offering advice and assistance to weaker ones before significant effort is expended. Projects that pass the pre-proposal stage and are ready for deeper consideration will receive feedback and questions, and will complete a four-page application, which expands on the information in the pre-proposal. In particular, at stage 2 the review focuses on: the unmet clinical need, the project goal(s), the innovative elements, and the methodologies, study design, milestones and timeline, outcomes, budget, and plan for future funding. In addition, "shovel-readiness" is very important as projects that are not likely to be commenced expeditiously are encouraged to re-apply when prospects for timely initiation are more favorable. To improve the timeliness of project completion and for more efficient tracking of outcomes, going forward, we will assign a Project Manager (see *Hub Research Capacity*) to each pilot award and milestones and timelines for the project will be jointly agreed upon and included in the project award notice. This practice has been critical to the success of other C/T pilot programs (see *C&C* component) and will improve our readiness to use National CTSA metrics when finalized.

Expansion. The centralized review of proposals will be continued and expanded in the coming five-year period (see Table 3); the University and other CTSC partners have had success in finding multiple new funding sources for C/T research programs from local, regional, national, and international stakeholders where the CTSC infrastructure provides a one-stop solution for assisting in the award of funds to meritorious applicants. The CTSC will continue as a broker for future interactions/opportunities, and for each program we will assess metrics of success not only on those who were funded but also those who were not. In many cases, our partnerships have gone beyond providing a review service and we often find powerful strategic alignments in joint funding selected C/T projects. Thus, for specific

Table 5: Committee Structure of CTSC Pilot Program

Committee	Members	Frequency of Meetings
Executive Committee	Strohl, Sedor, Kirwan and senior leaders of clinical research programs	1-2 per year
Steering Committee	Strohl, Sedor, Kirwan	Monthly
Large Pilot Review Committee	Ad hoc	1-2 per year as RFAs require
Core Utilization Pilot Review Committee	Ad hoc	Monthly

RFAs, we have provided joint funding from the CTSC when the partner pilot programs: promote basic and clinical investigator collaboration, support the movement of promising technologies to clinical testing, enhance the quality of science of pilot projects, and provide access to valuable core technologies and services in a collaborative and service-oriented fashion. We have supported joint funding programs and collaborations with NIH-funded research centers such as the National Center for Regenerative Medicine, the Skin Diseases Research Center and the Cystic Fibrosis Center. For these collaborations, we typically offer approval of Core Utilization pilots for grants supported by these centers, based on the outcomes of peer review.

Aim 2c: Promote team building through collaboration between C/T researchers and CTSC core facilities to encourage adoption of advanced technologies in C/T research through funding of Core Utilization Pilots

The core technology pilot applications are single page and are accepted monthly. The goal of the program is to build relationships between core facility director and staff and encourage adoption of advanced technologies to C/T research. Applicants are required to have consulted with relevant Core Directors, have all samples IRB and/or IACUC approvals in hand. Award decisions are made promptly by the review committee such that recommended projects can be started the next month. Unsuccessful applicants can re-submit once and receive a brief review and can consult with the Concierge and Steering Committee to identify weaknesses in their applications. Over 50 cores at the various institutions are approved to collaborate with applicants. Core facility retreats sponsored by CWRU and CTSC have attracted over 100 investigators each of the last three years and have helped investigators identify practical ways in which *TE* resources can enhance the quality, efficiency, significance, and impact of their research. The retreat outcomes have been published in newsletters and through our website. Many highly productive teams have emerged from these interactions and it has enhanced the connectedness of the Core directors to C/T research needs and opportunities.

NCATS Common Metrics: Publications and Grants. Tracking Annual Pilot awardee outcomes show that by 2016, 41% of awardees have published at least one scientific paper and 33% of awardees have received outside grant support in the same or related theme after completion of their pilot projects.

EVALUATION METRICS: TRANSLATIONAL ENDEAVORS			
Aim Area	**Measurable Objectives**	**Implementation of Strategies (Milestones)**	**Evidence of Success**
Aim 1: Expand and further integrate the Office of Translational Workforce Development (TWD) across the biomedical workforce continuum and link the workforce to enhanced educational initiatives	Develop, coordinate & evaluate educational resources while reducing training barriers	• Develop web and mobile technologies to coordinate & evaluate engagement of C/T workforce • Hire Translational Workforce coordinator • Hire educational consultants • Hire programmers/web developers	• > number URM in TR • > interest in TR careers • ↑# students trained • New web/mobile technologies • ↑# of innovations that improve translation
	Integrate, initiate and expand training efforts and education programs	• Mentor the trainees re: career gaps • City-wide Clinical Research Team Training Taskforce (CRTTT) streamlines & standardizes GCP training • Incorporate the I-Corps training curriculum into skills development programs • Expand graduate degree training with website, podcasts, workshops	• Enhanced mentoring/support faculty (validated survey: *C-Change*) • ↑% of investigators GCP-trained • ↑% investigators with I-Corps skills • ↑ Early stage projects moving forward toward commercialization • Regional & national expansion
Aim 1 &2: Enhance efficient technology solutions for TWD and PP	Expand use of Webgrants by new Pilot Programs	• Develop partnerships with CCCC, CFAR, CCDD, and NCAI Pilot programs	• ↑# Pilot LOIs • ↑# applications processed • # successful partnerships
	Develop unified web portal	• Unified web portal developed with access to training resources, documenting progress, ID strengths & gaps • Develop real-time tracking of progress	• ↑ usage of web portal by TR via web analytics • ↑# trainings in C/T • ↑# certifications • ↑ collaborations (survey users)
	Develop TransTrain App	• Pilot TransTrain App • Evaluate TransTrain App	• ↑ usage of TransTrain App • ↑ satisfaction of users
Aim 2: Advance translational science using pilot funding.	Develop targeted pilot studies	• Offer Methods Pilots • Offer Special Populations, Special Needs Pilots	• New methods developed • ↑ study subjects from URM, pediatric/geriatric subjects, studies on health disparities
	Develop multi-disciplinary teams	• High-technology core utilization pilots	• New collaborative teams • New technological innovations • ↑ Publications (Common metrics) • ↑ Grants (Common metrics)

E. Research Methods (RM)

SPECIFIC AIMS

Research Methods (RM) consists of two subcomponents: *Biostatistics, Epidemiology and Research Design* (BERD) and *Regulatory Knowledge and Support* (RKS). The BERD subcomponent is focused on providing CTSC investigators with guidance on optimal study design and analysis plans that lead to transparent and reproducible research. This includes developing and using novel innovative designs and analyses as needed. The RKS subcomponent is focused on assisting CTSC investigators with achieving and maintaining compliance with local, state and federal regulations specific to the responsible and ethical conduct of clinical and translational research. In addition, the RKS is also charged with assessing these processes, both within the CTSC and externally with other partner CTSA entities. These evaluations lead to the identification of potential inefficiencies and flexibility in the regulatory requirements that may streamline processes and provide a solid basis for increasing the number and type of research collaborations as well as leading to more efficient study start-ups. This ultimately will shorten the time for research findings to translate from bench-to-bedside and continue to impact best practices leading to improved patient outcomes. Thus the *RM* component focuses on the full spectrum of the clinical research process, from inception and design for BERD through study implementation for RKS, in order to advance team science and research in an efficient and ethical manner.

The overarching goal of *RM* is to lay the foundation for high quality research and data through the use and promotion of state-of-the-art biostatistics, epidemiology and regulatory support, including streamlined data capture systems such as REDCap, for clinical translational studies on a local and national level. The *RM* component through its two subcomponents and via collaboration with all other CTSC components will accomplish this goal through the following **general aims**:

Aim 1: Improve quality of research protocol submissions for internally funded projects (e.g., pilot studies) and applications for extramural support, to increase quality reproducible research outcomes and thereby decrease overall time to dissemination.

Aim 2: Create and support continuing education and workforce development opportunities for both novice and experienced clinical and translational research scientists and project personnel to (1) promote knowledge and application of effective clinical translational research design and methods, and (2) ensure adequate training for future generations of research professionals (e.g., medical students, residents, fellows, junior faculty and project personnel).

Aim 3: Collaborate with the other CTSC components, as well as with other CTSA Hubs, Trial Innovation Network (including the TICs and Recruitment Innovation Center (RIC)), to develop, leverage and disseminate knowledge and tools for enhancing clinical translational research.

Component Lead:

The *RM* component will be led by **Gerald Beck, PhD**, a biostatistician and staff member of the Cleveland Clinic's Department of Quantitative Health Sciences, has 40 years of experience collaborating with hundreds of clinical investigators on their individual research studies. He has been the Director of the CTSC BERD Core since 2007 for which the current proposal will be the continuation. Dr. Beck has over 30 years of experience leading or participating in Data Coordinating Centers for NIH supported multicenter clinical trials and observational studies, particularly in kidney and pulmonary disease. Currently, he is the Principal Investigator of the Data Coordinating Center (DCC) for the NHLBI supported Pulmonary Vascular Disease Phenomics (PVDOMICS). Coordinating multi-center studies has made him very knowledgeable of regulatory policies and needs at a variety of institutions beyond the Cleveland Clinic. He has served on many DSMBs for NIH and VA supported studies. He is a Fellow of the American Statistical Association and the Society for Clinical Trials.

Dr. Beck will provide overall direction for the *RM* component, as well as direct oversight of BERD. Working closely with **Philip Cola, PhD**, who is responsible for RKS, Dr. Beck will interface with CTSC leadership and other components on all administrative issues relating to *RM*. Dr. Beck will participate as the *RM's* liaison to the CTSC Evaluation Program and will be responsible for the implementation of data collection tools and oversee the result compilation and communication for evaluative reports. See the Evaluation Metrics tables for BERD and RKS below. In conjunction with Dr. Cola, Dr. Beck will prepare the RM annual reports.

RM: Biostatistics, Epidemiology, and Research Design (BERD)

Goal: BERD's primary goal is to encourage and expand CTSC-wide inclusion of statistical and epidemiological collaborations in translational research studies. Including methodological experts in these **collaborations/consultations** ensures that investigators clearly delineate their research questions and objectives and consider appropriate study design and statistical analysis plans well in advance of study implementation. In the last 9 years, the BERD has collaborated on more than 1400 studies. In addition to statistical consultations, BERD members are actively engaged in the **development of novel study designs and statistical methods** to enhance and promote translational research across Cleveland as well as the entire CTSA. Recognizing the importance of a solid understanding of epidemiological and statistical methods, BERD members are committed to the growth and development of formal and informal **education** to investigators through degree/training programs, courses, workshops, seminars and mentoring. To address the three distinct areas of collaboration, formal and informal education, and development of novel study designs and statistical methods, the **specific aims** for the BERD sub-component are:

Aim 1: To collaborate with CTSC investigators to ensure use of optimal study designs and appropriate development of statistical analysis plans.
Aim 2: To educate and mentor investigators in study design and statistical analysis methods.
Aim 3: To develop novel study designs and statistical methods for clinical translational research.
Aim 4: To collaborate with local CTSC components and other CTSC Hubs to leverage resources and disseminate BERD innovations within the context of the appropriate regulatory framework.

BERD Leadership: Support to meet our four aims will be coordinated under the direction of the current BERD leadership consisting of three faculty members at the academic biostatistics/epidemiology homes of CTSC: **Gerald Beck, PhD** (CC), Director of BERD; **Sara Debanne, PhD** (CWRU/UH), Co-Director of BERD; and **Douglas Einstadter, MD, MPH** (MH), Co-Director of BERD. The Department of Quantitative Health Sciences, Cleveland Clinic consists of four sections: Biostatistics, Clinical Trials Design and Analysis, Health Outcomes Research and Clinical Epidemiology, and Statistical Genetics and Bioinformatics. The Department of Population and Quantitative Health, CWRU SOM consists of 5 divisions: Genetic Epidemiology and Biostatistics; Global Health Epidemiology; Health Behavior and Prevention; Health Care Organization, Outcomes and Policy; Modern Biostatistics. The Center for Health Care Research and Policy, CWRU, MetroHealth consists of 5 divisions: Population Health, Biostatistics and Evaluation, Health Economics and Policy, Health Care Informatics, and Education and Training.

Aim 1: To collaborate with CTSC investigators to ensure use of optimal study designs and appropriate development of statistical analysis plans. Our goal is to improve the quality of research studies and increase funding probability for investigators using the CTSC. While improving, presently, many studies are planned or commence with no or minimal involvement of a statistical or epidemiological expert. For example, at CC <9% of the more than 3800 annual journal publications involve a statistician. Translating important clinical questions into scientifically sound studies requires skillful, creative, and thorough epidemiological and statistical planning within the constraints of limited time and resources. Over the past nine years, the primary mission of the BERD has been to provide expertise for protocol development. In order to continue and enhance this support, the BERD will: 1) provide a streamlined process for timely access to collaborative support; 2) further enhance BERD collaboration via interaction with other CTSC components; and, 3) conduct ongoing evaluation of BERD collaborative activities. We have identified three key phases for utilizing BERD collaborative support (Figure 1).

Phase 1a: Initial Contact. To enhance our presence, especially among those investigators currently unaware of the BERD or new to our CTSC, we will maintain a regularly updated BERD page on the CTSC website to describe available support, give contact information, and describe new initiatives/activities. The CTSC Research Concierge along with the new case management system will assist in familiarizing CTSC investigators with BERD resources. Other methods to facilitate initial contact with BERD will include brochures and targeted seminars describing BERD services (protocol development, education and novel methods development, support mechanisms, and points of access) as well as "speed dating" (consulting) sessions with investigators who are developing research ideas.

Figure 1: Streamlined process for timely access to BERD collaborative support.

Phase 1b: Initial Study Review. In response to a request for assistance, a BERD contact will arrange for an initial meeting to review the planned study protocol and determine the appropriate type and amount of support required. To leverage the diverse epidemiological and biostatistical expertise available at CTSC institutions, the BERD will create, maintain and distribute a roster of statisticians and epidemiologists and their expertise to aid in identifying appropriate faculty or staff for a given protocol. A skill-finder link on the BERD web page as well as Pure Experts will be available to help users identify relevant experts.

Phases 2 and 3: Collaboration to Develop a Design and Analysis Plan. The collaboration between the investigator and the appropriate identified BERD faculty/staff will address epidemiological and statistical issues. The goal will be to develop a sound and pragmatic study design with an estimate of sample size and power and a detailed statistical analysis plan that ensures that the study can adequately address each hypothesis. These can lead to an increased likelihood of having quality reproducible research. BERD activities during protocol development will be funded by CTSC and/or direct institutional funds. The investigator will be expected to include funding in their grant for ongoing epidemiological and biostatistical support to ensure development of appropriate databases and case report forms, supervision of data collection and data management, performance of statistical analyses, and participation in abstract and manuscript generation. The BERD collaborator(s) will work with the investigator during the study's protocol development to determine the appropriate level of grant funding required for the above activities. These collaborations have been initiated in alignment with the preliminary recommendations of the "Scientific Review Committee" national initiative (e.g., 12 participating Hubs including the CTSC – see RKS section below).

Aim 2: To educate and mentor investigators in study design and statistical analysis. Our goal is to improve investigator knowledge and promote higher quality research within Cleveland. Clinical investigators conducting translational research require a solid understanding of statistical and epidemiological thinking. Achieving functional collaboration and effective teamwork in the conduct of multidisciplinary science requires that all members of the team contribute to the decisions that go into building an effective study design and analytic plan, rather than abdicating this responsibility solely to a statistician or epidemiologist who may lack substantive expertise in the clinical area. As part of the vibrant learning environment for aspiring and veteran clinical investigators envisioned by the CTSC, the BERD will work with other CTSC components (e.g., the Office of Translational Work Force Development (TWD) – see their Figure 1) to: 1) Raise awareness of and facilitate access to educational opportunities within CTSC institutions and beyond; 2) Provide user-friendly education courses; 3) Develop new programs and expand local educational opportunities; and 4) Use innovative approaches (e.g., on-line, interactive, mobile apps, massive open on-line courses (MOOCs). BERD and CTSC educational efforts will continue to focus on bringing smart, modern thinking on statistics, epidemiology and related issues of study design to non-statistician clinical investigators through degree/training programs, courses, workshops, seminars and mentoring in epidemiology and biostatistics. We will share best practices on education and training across our CTSC institutions and nationally (see Aim 4), and expand continuing education opportunities for BERD and CTSC investigators.

Aim 3: To develop novel study designs and statistical methods for translational research. Our goal is to foster improved study designs, analyses and integration of research and clinical care leading to higher quality and more effective translation of science to the population. The development of novel methods is relevant to many CTSA investigators both locally and nationally. The over 70 faculty biostatisticians and epidemiologists across the CTSC institutions who are actively involved in the development of innovative methodologies relevant to translational research will catalyze the development of novel methods. Examples of such methods include, adaptive clinical trials, N-of-1 trials, dynamic treatment regimens, causal inference, bioinformatics with its rich (but complex) –omics, functional data analysis, measurement error models, and cost effectiveness research. To accomplish this aim, we will: 1) promote the use of appropriate methodologies in translational research (e.g., Institute of Medicine's Learning Health Systems); 2) solve problems and address barriers that impede conduct of clinical and translational research; 3) develop new approaches motivated by problems encountered in translational research; 4) participate in core utilization pilot studies; and 5) involve all local academic research sections (CWRU, Cleveland Clinic, MetroHealth) in the development of novel tools and methods.

We will disseminate new methods (Goal 1) to the wider CTSC community by including on the BERD website recent publications and working papers by BERD members describing newly developed methods. Two recent examples of our solving problems (Goal 2) and developing new approaches (Goal 3) are: 1) improving the prediction of hospital inpatient vital sign alerts for cardiopulmonary arrests by using EHR data which increased the area under the Receiver Operating Characteristic curve from 0.71 to 0.83 (Dr. L. Jehi), and 2) developing a prediction model and nomogram to provide individualized predictions of seizure outcomes after epilepsy surgery

at the CC.[1] Four other institutions have subsequently validated this model. We will also promote journal clubs and seminars at the CTSC institutions. We will emphasize topics of interest to our CTSC, such as methodology related to community interventions (e.g., cluster-randomized trials) and T1 research. We will announce relevant seminars and journal clubs on the CTSC BERD website and may make them available to the wider CTSA community via webinars. We will also use metrics acquired in Aim 1 to track protocol development to identify topics that would be particularly relevant to the CTSC (Goal 3). Goal 4 (pilot studies) are described in the Translational Workforce Development section (Section D). Investigators may apply for funding to support development of novel translational methods where BERD members are part of, or even lead, the research team, or apply on their own for statistical/epidemiological methods development. These activities will involve the three CTSC academic biostatistics/epidemiology departments described in the Introduction (Goal 5) and will help in the mentorship of investigators at all levels.

Aim 4: Collaborate with CTSC components and other CTSA Hubs to leverage resources and to disseminate BERD innovations. For BERD Aims 1-3, and the aims of other CTSC components, effective collaboration is essential. The BERD will actively seek collaboration with other Cleveland CTSC components/internal groups, other CTSA Hubs, as currently with the Ohio Consortium of CTSAs (see TWD) in developing and participating in multi-site studies, and sharing data and information, and external groups (e.g., Ohio Clinical Trials Collaborative (OCTC), and professional societies such as the Association for Clinical Translational Science (ACTS) and their BERD Special Interest Group. Additionally, the BERD will work to leverage resources within and among groups, disseminate work, tools, information, etc. and integrate evidence-based interventions into practice settings. The BERD will collaborate with other CTSC components to enhance each aim: *Informatics* to identify potentially eligible study patients, use appropriate data management systems and warehouse data that can be shared. *Translational Endeavors* to assist researchers on novel methods and do pilot studies. *Hub Research Capacity,* which has the goal of integrating the components and is the first point of contact (see HRC). *Network Capacity and Community and Collaboration* to identify study team members and expedite the implementation and recruitment performance (through the Trial Innovation Network (and its Recruitment Innovation Center-RIC) and its Trial Innovation Centers-TICs) – see *Network Capacity*.

EVALUATION METRICS: BIOSTATISTICS, EPIDEMIOLOGY AND RESEARCH DESIGN			
Aim Area	**Measurable Objectives**	**Implementation of Strategies**	**Evidence of Success**
Aim 1: Collaboration with CTSC investigators	Provide design and statistical support for investigators; encourage investigators to submit grants	• Use existing BERD related methods and metrics as in Rubio et al., 2011[2] • Create study teams • Include BERD members as co-I • Help design studies • Assist in grant preparation	• # investigators served • ↑ # of assisted projects by at least 10%/yr • # grants submitted • ↑ percentage of funded projects each year • ↑ # CTSC-based publications each year
	Investigator satisfaction	• Measure client satisfaction via survey at end of each collaboration.	• ↑ average satisfaction scores each year
Aim 2: Educate and mentor CTSC investigators	See those in TWD Section	• As in TWD Section	• As in TWD Section
	BERD faculty design or teach courses, workshops, seminars	• Teach BERD courses • Give BERD seminars, workshops • Survey BERD faculty on their educational activities on type of and level of involvement	• ↑ activities each year • % BERD staff who teach • # students taught • # courses taught • Course evaluations
	Mentor students in proper research design and analysis methods	• Determine mentor and mentee satisfaction via surveys	• # students mentored • ↑ satisfaction of students and mentees • Competencies achieved by students
	BERD faculty involved in national educational programs and publications	• Serve on national committees • Publish educational activities • Survey BERD faculty on their national educational activities	• # and types of educational activities • # educational publications • ↑ activities each year
Aim 3: Develop novel study designs and statistical methods	Develop novel methods and designs	• Encourage BERD faculty to develop relevant new methods • Use existing BERD related methods and metrics as in Rubio et al., 2011	• # and type of new methods in collaborations
Aim 4: Leverage and disseminate BERD innovations	Collaborate within CTSC components and with CTSC Hubs to disseminate innovations	• Partner with other CTSC Hubs, particularly in Ohio • Collaborate with the Ohio Clinical Trial Collaborative	• # partnerships locally, regionally or nationally • Level of activity
	Participation in national professional groups	• Participate in ACTS BERD SIG	• Types and Level of activity in prof. groups

RM: Regulatory Knowledge and Support (RKS)

Goal: The goal of the RKS is to support high quality, reproducible research across the spectrum of clinical and translational sciences by identifying efficient and cost effective ways in which to promote adherence to regulatory requirements and overall responsible conduct of research. In previous years, the RKS focused on: a) identifying common concerns related to the oversight of translational research, including institutional review processes perceived by investigators as "burdensome" and/or "redundant" and b) defining and pilot testing new workflows, standard metrics, comprehensive research education and opportunities for inter-institutional collaboration. While these efforts have promoted vital discourse between major local research entities in Cleveland, additional steps must be taken to translate these process improvement theories and pilot work flows into actionable items capable of supporting research network expansion, thus increasing the amount of "bench-to-bedside" and "bedside to community" research. The RKS has outlined three aims that will help synthesize its own unified efforts with those individually taken by CTSC partners to form a more centralized process improvement plan. These aims will encourage partnerships with regional and national CTSA entities as well as those not affiliated with CTSA (including for-profit entities and industry) and provide opportunities for workforce development to support more collaborative science efforts and quicker translation into community settings.

Aim 1: Harmonize cross institutional policies and infrastructure to improve the quality of human subject protections and promote a clear culture of responsibility among CTSC investigators

Aim 2: Streamline regulatory review process to promote research collaboration, which will facilitate translation of scientific ideas to clinical practice

Aim 3: Provide formal innovative educational opportunities (e.g., certificate program) in Regulatory Sciences to complement and extend existing CTSC Regulatory offerings to members of the translational workforce

RKS Leadership: The RKS will accomplish these aims under the direction of **Philip Cola, PhD** (Case Western Reserve University), Director of the RKS and **Carey Gorden, JD** (MH), co-Director of RKS. Support efforts will be will be carried out by partner staff at each collaborative institution: **Joan Booth** (CC), **Carolyn Apperson, MStat** (CWRU), **Carey Gorden, JD** (MH), and **Jenna Stump, MS** (UH). **Kathy Lawry, MSSA, CIP** (retired from MH) will continue as the SMART IRB Ambassador regionally and for the CTSC.

Aim 1: Harmonize cross institutional policies and infrastructure to improve the quality of human subject protections and promote a clear culture of responsibility among CTSC investigators The CTSA, both on a national level and locally under the CTSC partnership, has made significant strides in identifying and addressing inefficiencies in the federally mandated research review process.[3] However, continued focus on national level integration of these streamlined regulatory processes is essential as new technologies and therapies are developed and require rigorous scientific testing. This is consistent with the recent call to action promulgated by the IOM and NCATS and the proposed HHS Federal Notice of Proposed Rule Making (NPRM). During this project cycle, the RKS will focus on innovations in the area of participant protections to promote regulatory competency (e.g., SMART IRB initiative). The RKS will utilize the existing workgroup structure, current regulatory guidance, NIH Notice of Proposed Rule Making (NPRM) suggestions and new technologies to a) improve the consent process and b) promote responsible access to clinical trials data and biospecimens to support transparency of results and secondary use in a regulatory compliant manner.

Although the informed consent process was developed to "protect" the research participant by ensuring that the individual was provided all information needed to make an informed decision about participating in a research project, subsequent years have seen this process become cumbersome as research institutions react to high profile instances of lack of information/misinformation in the consent form document. The RKS will work with CTSC investigators and local research administrators to refine the informed consent process while maintaining compliance with 45 CFR 46 and 21 CFR 50 requirements. The RKS will achieve this by (a) assessing current state of the consent process across the spectrum of clinical trials conducted at CTSC partner institutions (b) reviewing ways to shorten written form by simplifying overly complex standard medical and legal jargon and (c) promoting utilization of technology to supplement the consent process and enhance subject comprehension. Pilot tests of short form consent documents, use of electronic consent processes and use of supplemental consent information such as video presentations, as well as use of technology during the research participant experience (as a source of information about the trial and as a method of data capture about the overall consent process and qualitative survey about participant comprehension) will take place. Evaluation of impact to consent process will be done primarily in conjunction with BERD and Evaluation (*Administrative Core*) to assess how the

changes impact the consent process and participant comprehension. These activities in human subjects protections include participation from the Cleveland VA.

The RKS will also support local and national level efforts to promote access to clinical trials data and biospecimens to support transparency of outcomes and secondary use. Currently the CTSC partner institutions are developing methods to promote the use of data and biospecimens through use of opt in/out sections within both clinical and research consent forms. During the project period, the RKS will promote development of standardized "biobanking" consent language to be used by CTSC investigators across institutions. In addition, through a partnership with the CWRU Institute for Computational Biology, CTSC partners will have access to a central data repository within which local clinical trials data will be stored. This database will provide a storehouse of individual and population based health information to be shared in a de-identified manner in a HIPAA compliant way for internal and external secondary analysis.

Aim 2: Streamline regulatory review process to promote research collaboration, which will facilitate translation of scientific ideas to clinical practice This aim will focus on ***integration*** of the best research management practices into the clinical trial process to facilitate regulatory compliance in an efficient manner.[4] The RKS proposes centralization of research administration services for CTSC to encourage Phase I investigator initiated clinical trials as well as broader community based health outcomes research. The RKS will work with *Hub Resource Capacity* and *Network Capacity*, as well as Recruitment Innovation Centers (RICs) to develop master agreements for multi-site studies, promote efficiencies of contracting and human subject protection reviews, and support discussions surrounding regulatory centralization. Improved informatics will promote networking of sites to support multi-center evidence based outcomes research in a more efficient manner. This will increase the subject pool and theoretically decrease time to study implementation, thereby encouraging more rapid dissemination of results within the community.[5]

The RKS will continue to support ***Collaborative Engagement*** with external partners encouraging shared regulatory process and data/information platforms to support clinical trial regulatory activities. Early accomplishments were seen locally through the development of a city-wide IRB "facilitated review" network, which was developed as a way to reduce the cost of conducting human subjects research through multi-center research. In recent years, CTSC's local network has evolved into a regional consortium of CTSC partners within the Midwest. Nationally the RKS is bringing our own reciprocal review expertise to the NCATS national IRB "reliant review" pilot project (IRBRely) led by Dartmouth University. During the current project period, the RKS will continue to support research network growth by strategically adding sites (CTSA and non-CTSA affiliated) to the Midwest Regional Reliant Review Network and track outcomes of participation. These outcomes will be used to support sustainability effort as core institutions of national reliant review (CWRU, Harvard, Dartmouth and University of Wisconsin) are seeking various partnerships with NCATS to support continued growth. Building on success with centralization of IRB review processes, the RKS is participating as one of 12 CTSA sites identified to pilot test a unified "Scientific Review Committee" framework, designed to streamline scientific review processes, confirm scientific validity and feasibility of proposed clinical research trial in a meaningful way so as to have impact, or in some cases even reduce, time required to complete IRB review processes. Both initiatives will lay the groundwork to support upcoming changes in HHS regulation requiring research review centralization for multicenter clinical trials.

Another way that RKS supports collaborative engagement is through the pilot test of the eRegulatory tool known as Complion, which provides a user-friendly environment for investigators to easily submit drug and device applications to the FDA. Complion also provides investigator/sponsors an electronic environment to maintain FDA compliant regulatory review documents. During the pilot period, the RKS collected qualitative information from local investigators that indicated that regulatory burden for investigator/sponsors was "too great" for many researchers, who often have minimal funds and staff resources at the time of application. The RKS promoted the FDA Core as the home for this regulatory binder software to support submissions that otherwise would be abandoned. During the two-year pilot period, the number of new investigator/sponsor applications submitted to the FDA for review and approval increased 20%. Based on this success, the RKS will expand system access more broadly to CTSC investigators as well as local investigators conducting studies not directly related to the CTSC to support and accelerate investigator IND/IDE process. Streamlining the oversight of long term maintenance for electronic regulatory files and long term monitoring through the FDA Guidance Core will support cost efficient regulatory compliance locally and facilitate the progression of phase 1 trials to market. Each of the activities mentioned in AIM 2 are based on CTSC new implementations and are not merely additive to previously existing regulatory program activities.

Aim 3: Provide innovative educational opportunities in Regulatory Sciences to complement and extend existing CTSC Regulatory offerings to all members of the translational workforce Education and training for the CTSC research community continue to support a collaborative environment between researchers and regulatory staff, finding more ways in which to work together to promote responsible conduct of research. Many efforts such as IRB "office hours," in which IRB staff meet with research staff prior to IRB submission to review new protocols prior to submission, and mandated research staff regulatory training, in which research staff are trained by institutional compliance monitoring staff to develop a partnership to support clinical trial conduct, are resulting in quicker study completion times (through improved IRB review times and better compliance monitoring outcomes). The RKS will continue to examine new and innovative ways to reach investigators with necessary information regarding regulatory compliance topics for clinical and translational research, looking to increase participation in these offerings during the next phase of our CTSA award. The RKS will also take the training to the next level to provide more comprehensive and innovative structured offerings to train the next generation of research professionals. The RKS has created formal educational course offerings in Leadership Assessment and Development (CRSP 502) and Managing Research Records: A Systems Approach (CRSP 504). Additionally, development of 3-5 more courses is underway. These include 1) FDA Regulatory Management 2) Human Subjects Protection and Clinical Research Compliance 3) Grants Management 4) Entrepreneurship/Technology Transfer and 5) Workforce Development. These are expected to culminate in a Certificate in Research Management or Regulatory Sciences that will be offered to past or current KL2 scholars and to students in the Master's or Doctoral clinical research programs that are part of the CTSC. The two existing courses are offered in the Clinical Research Scholars Program (CRSP) with strong enrollment. This detailed formal research education and training will directly complement BERD Aim 2 Translational Workforce Development by training research professionals to conduct research according to local, state, and federal requirements. The RKS will provide on-site internship programs for local CTSC sites and work locally to link educational programming across CTSC components and allow for national development among translational science centers. In addition, the RKS will explore innovative approaches towards information sharing such as on-line, interactive courses to expand the reach to meet the needs of the research community and increase retention of highly trained research professionals and potentially the use of on-line investigator resources such as "Frequently Asked Questions" (FAQs) and community blogs/information pages to discuss general topics related to human subjects research and maintaining compliance with the regulations.

NCATS Common Metrics: IRB Duration: From 2013 to 2015, Our IRB approval time was reduced from a median of 52 days to 34 days.

EVALUATION METRICS: REGULATORY KNOWLEDGE AND SUPPORT		
Measurable Objectives	**Milestones**	**Evidence of success (Metrics)**
Aim 1: Improve the consent process	• Improving comprehension through simplification	• Shorter consent forms • Assess comprehension via qualitative survey
	• Electronic consent processes	• # subjects enrolled with e-consents
	• Shortened physical forms with supplemental information such as video presentations	• Supplemental consent info in alternative formats • Qualitative improvements in consent process
Aim 1: Promote access to clinical trials data and biospecimens	• Study enrollment and participation via "app" with electronic clinical data capture	• ↑ in # and use of biospecimens
	• Partner with ICB to design & build a clinical trial data repository	• # of studies with trial data maintained in the centralized database and use of outcomes data
Aim 2: Provide centralized research services	• Master agreements for multi-site studies	• ↑ multi-site studies w/ master agreements
	efficiencies of contracting	• ↓ submission to site initiation time
	• Human subjects protection reviews	• ↓ IRB approval time (Common Metric)
Aim 2: Collaborative engagement	• Informatics will promote networking of sites	• ↑ of CTSA sites participating in network
	• Add sites to IRB Reliant Review Network	• ↑ new sites in current Reliant Network • ↑ national partnerships of other Reliant networks • ↑ Reliant review protocols
	• Pilot a unified Scientific Review Comm. framework	• ↓IRB review time
	• Expand Complion eRegulatory tool to new sites (new CTSAs? CTSC partners?)	• ↑ investigators using Complion
Aim 3: Develop new programs in regulatory science	• Develop core curriculum for Certificate and/or Master's Program in Research Management or Regulatory Sciences	• # of participants (enrolled vs graduated) • # of Certificates granted • # of classes/workshops/courses offered
	• On-site internship programs for local CTSC sites	
	• Expand delivery to on-line, interactive courses	

F. Hub Research Capacity (HRC)

SPECIFIC AIMS

Hub Research Capacity (HRC) will facilitate timely and responsible completion of human studies, particularly those requiring recruitment of populations that are difficult to reach (**Integrating Special Populations [ISP]**), and those with complex protocols (**Participant and Clinical Interactions [PCI]**). Use of the *HRC* enables investigators to: 1) access diverse study populations and experienced research personnel; 2) utilize dedicated and standardized research facilities and environments, and 3) implement continuous and purposeful quality improvement processes for research studies. The ultimate goal is to lead projects from conception through completion, and to effectively disseminate key findings through responsible and reproducible research. Target Users: We envision two main types of investigators utilizing *HRC*: 1) funded investigators that request specific facilities/equipment or services offered; 2) investigators (particularly translational or early-career scientists) that seek help with co-management of human studies (usually involved at the funding solicitation stage) from concept/project development and start-up to study execution and closure/results dissemination. We envision solicitations for guidance with studies that require assistance in research quality improvement or those struggling with participant recruitment. *HRC* will maximize impact via a catalytic approach: developing, demonstrating utility of, and then disseminating improvements in translational science and operations. The *HRC* closely integrates services with all other components of the Hub, and will incorporate standardized National CTSA metrics into its processes to evaluate success.

Integrating Special Populations (ISP)

Aim 1: Pair investigators with Participant Recruitment Specialists and Point Persons, to engage special populations in new proposal and ongoing research studies.

Aim 2: Facilitate investigator training and access to existing, underutilized recruitment tools to better integrate special populations and achieve full enrollment.

Participant and Clinical Interactions (PCI)

Aim 1: Oversee and assure quality environments (personnel, facilities and equipment) for the conduct of funded research.

Aim 2: Provide project stewardship and oversight for an entire project's lifecycle, from idea conception through study closure and dissemination of results.

Aim 3: Broaden participant recruitment processes, in general, with digital tools to increase efficiencies and decrease cost of recruitment.

Challenges of Human Research and Proposed HRC Solutions

	Challenges	Proposed HRC Solutions	Target
Integrating Special Populations (ISP)	Inadequate Inclusion of special populations	• Participant Recruitment Specialists (PRS) • Protocol review process and partnering with Community & Collaboration to use the Special Populations and Dissemination Consult Service to identify "best practices" for inclusion of diverse/underrepresented populations • Diversity recruitment checklist • Establish recruitment resource: Point Persons for Special Populations	All studies
	Limited use of tools to identify special populations	PRS will: • Educate investigators to assess and create recruitment plans • Partner with Informatics to ensure availability of investigator training in use of recruitment tools.	All investigators
Participant and Clinical Interactions (PCI)	Research resources	• Multi-disciplinary protocol review process: quality assessment of protocol viability for implementation and budget • Facilitate access to quality research facilities, equipment and staff	All studies
	Study execution	Research Acceleration Management Partnership (RAMP). Proactive expert project management guidance/quality oversight for: • Concept/Project Development • Project Start-up • Project Execution • Project completion/Results dissemination	All CTSC studies (including CTSC Pilot studies)
	Study execution	• Novel Recruitment Strategies: increased use of digital tools to speed identification and solicitation of eligible study participants	All studies, by request

Component Lead: *HRC* will be led by **W. H. Wilson Tang, MD.** He has been a driving force in bringing relevant new services to clinical researchers. Dr. Tang leads the NIH-sponsored Heart Failure Clinical Research Network that has utilized CTSA Hub services to achieve enrollment targets and deliver quality data. Dr. Tang will also lead the PCI sub-component of *HRC*. The ISP sub-component of *HRC* will be led by **Patrick Catalano, MD** who focuses on minority and socio-economically underserved populations. He is a maternal-fetal medicine physician at who has directed clinical research resources for over 25 years.

HRC: Integrating Special Populations (ISP)

Goal: The goals for ISP ensure the systematic integration of diverse participant populations across clinical research studies. Expanding upon existing well-developed and knowledgeable integration of special populations, we are instituting systematic approaches and support systems to further improve integration of special populations into the Cleveland CTSC. Investigators with special knowledge will serve as Point Persons (Table 1) to help other investigators address major recruitment challenges. The *HRC* ISP aims, along with *Network Capacity* and community partners, to facilitate inclusion of a wider base of participants in research studies to generate results that are applicable to a broader population.

ISP Leadership: This sub-component will be led by **Patrick Catalano, MD** who will facilitate investigator access to Point Persons. Dr. Catalano's women's health research focuses on minority and socio-economically underserved populations; he understands recruitment challenges in greater Cleveland. He is a maternal-fetal medicine physician at MetroHealth who has directed clinical research resources for over 25 years. ISP is co-led by **Grace McComsey, MD***,* an adult and pediatric infectious diseases specialist, with a research focus on HIV infection, particularly in children; and **W. H. Wilson Tang, MD**, a cardiologist who has led EHR recruitment tool use and has accessed the Amish of NE Ohio for research participation. All three are clinical translational scientists who have successfully led multiple clinical studies including those enriched for special populations..

Approach: *Challenges:* The lack of inclusion of special populations in research limits generalizability of results. Projects that study common diseases (like asthma, heart failure, hypertension, obesity, diabetes) often neglect that lifespan, gender, racial/ethnic diversity and socioeconomic disparity are major determinants of disease course and outcomes. Two major recruitment challenges are:

- *Inadequate inclusion* – When special populations are under-represented in research study design, study findings lack generalizability. Investigators may limit populations in an effort to minimize confounders, such as age and medical conditions, with narrow inclusion/exclusion criteria that may be too stringent.
- *Limited use of tools for identification* – Informatics recruitment tools exist but study teams lack awareness and training to optimize their use to identify and recruit special populations. Along with these tools, best practices and strategies are needed to identify, recruit, and retain special populations.

We propose a two-pronged approach to address these challenges across the CTSC:
Aim 1: Pair investigators with **Participant Recruitment Specialists** and **Point Persons**, to engage special populations in new proposals and ongoing research studies.
Aim 2: Facilitate investigator training and access to existing, underutilized recruitment tools to better integrate special populations and achieve full enrollment

Aim 1: Pair investigators with **Participant Recruitment Specialists** and **Point Persons**, to engage special populations in new proposals and ongoing research studies that desire more inclusive enrollment.
Innovations/New programs: In Aim 1, we will directly tackle the "inadequate inclusion" challenge and propose to proactively identify recruitment needs across the lifespan and diversity. We will establish **Participant Recruitment Specialists (PRS)** to serve as ISP facilitators for studies. They will advocate and liaison with community groups and *Community & Collaboration* to assist investigators to identify special populations in grant proposals or protocols to broaden the generalizability of research results. PRS will institute a protocol review process and best practices for new and ongoing research studies in the Hub to help identify and include diverse and underrepresented study populations. The protocol review process includes a Diversity Recruitment Checklist to appraise plans for including a wide range of populations, as well as strategies for gender and racial/ethnic diversity. The PRS will work with investigators to modify study designs or recruitment approaches to ensure broader inclusion of research participants. Second, the PRS identifies and builds relationships with the identified **Point Persons for Special Populations,** guides investigators to the Point Persons and facilitates their interactions to access "missing" populations. The *Hub Research Capacity* component within ISP offers a **Special Populations and Dissemination Consult Service**, led by Ashwini Sehgal, MD, Co-Director of the CWRU Center for Reducing Health Disparities at MH. This represents one such point-of-contact service available to assist the investigator and PRS to create a plan and strategize best practices to conduct research in community settings, with input of community members or community organizations. Involving communities in this manner can help researchers understand community priorities, refine research questions, increase recruitment and retention, and enhance the likelihood that findings will be translated into improvement of healthcare for all. PRSs will also identify additional opportunities (such as health fairs, access to community resources and public events, or contact with government liaisons) to facilitate inclusion of special populations.

Point Persons are local CTSC investigators, with knowledge of special populations and recruitment barriers who have surmounted these challenges. Point Persons (see Table 1) will advise and assist investigators in creating recruitment and retention strategies for a wide range of populations and aid investigators in establishing best practices to assure an increased range of study populations across the lifespan and with cross-sectional differences.

Table 1: Point Persons

Special Population	UHCMC	MHMC	CC
Child Health / Pediatrics	Michael Konstan, MD James Chmiel, MD	Nazha Abughali, MD	Katherine Dell, MD
Community & Collaboration	Elaine Borawski, PhD.		
Geriatrics	Stephan Gravenstein, MD	James Campbell, MD	John Kirwan, PhD
Health Disparities	Margaret Larkins-Pettigrew, MD	Ash Sehgal, MD	Charles Modlin, MD
Women's and Perinatal Health	Honor Wolfe, MD	Pat Catalano, MD Edward Chien, MD	Amy Merlino, MD
LGBT	Grace McComsey, MD	Henry Ng, MD	
African American Males	Jackson Wright, MD, PhD	John Sedor, MD	Charles Modlin, MD
Rare Disease: Vasculitis	Elizabeth Brooks, MD, PhD	Nora Singer, MD	Heather Gornick, MD
Severe Asthma	James Chmiel, MD Kristie Ross, MD	Ted Warren, MD	Serpil Erzurum, MD
Amish	Shawn McCandless, MD	Mark Dunlap, MD	Wilson Tang, MD
Spinal cord injuries	John Chae, MD, ME and Frederick Frost, MD		
Veterans	Kingman Strohl, M.D.		

Integrate with Existing and New CTSA Hubs nationally for including Special Populations in multi-site Trial Innovation Network (TIN) studies: Our local experience both as participants and leaders of large, multi-site trials positions us, through *Network Capacity*, to be active participants in national TIN studies. We are already actively participating in the rollout of our local Trial Innovation Unit processes. The large cadre of investigators in Table 1 already work with special populations and will be significant contacts for the national network of CTSA Hubs. The ISP element will utilize tools and best practices from the CTSA Recruitment Innovation Center.

Aim 2: Facilitate investigator training and access to existing, underutilized recruitment tools to better integrate special populations and achieve full enrollment

Challenge: Study designs lack robust recruitment plans. Informatics Core recruitment tools exist but study teams lack awareness and training to optimize their use to identify and recruit special populations. *Innovation*: PRSs will educate investigators to assess and create recruitment plans. PRSs will work with *Informatics* to ensure availability of investigator training in use of recruitment tools to: 1) perform feasibility assessments with *Informatic's* CLEARPATH, Explorys® and other EHR-based tools, using approved IRB language; 2) expand sign-up campaigns for ResearchMatch® strategically-launched to specific populations; and 3) increase outreach to potential participants via web portals and EHR communications by providing enhancements to the Knowledge Program® (KP) to send protocol-specific inclusion/exclusion surveys. *HRC* will expand access and applicability of these tools across other CTSA Hubs via the *Network Capacity* liaison to Trials Innovation Network (TIN).

Tools for HRC Recruitment Efficiency

Web and Platform-based Tools:	Description:
ResearchMatch®	Online access sign-up for research participation and match for research studies
Explorys®	Self-service EHR feasibility review for enrollment criteria and special populations
Informatics support	EHR-based integrated database tools (CLEARPATH and SHED) to capture data and manage queries for participant recruitment (i.e Epic and Allscripts)
Knowledge Program®	Outreach to clinical population for potential study participation, directly embedded to EHR or web/email access
NetWellness	A "Person-Centered" online communications interface for special population outreach. Using web and social media strategies, provides platform for recruitment outreach and dissemination of research results to both general and special populations audiences.

HRC: Participant and Clinical Interactions (PCI)

Goal: The primary goal for Participant and Clinical Interactions (PCI) is to successfully manage the quality of translational research projects. Investigators depend upon knowledgeable planning, estimation, and stewardship of resources, facilities/environment and staff required for all aspects of study conduct. PCI delivers ready access to quality research environments and resources and offers an innovative process to oversee successful research completion – the new Research Accelerated Management Process (RAMP). Led by

Research Quality Managers, the RAMP process is executed by **Research Navigators**, **Project Managers** and **Participant Recruitment Specialists**. The use of a standardized process for project management builds a foundation of reliable and dependable workflows, thereby promoting quality, efficiency and successful completion of research projects. PCI also increases access to electronic recruitment methods to overcome recruitment obstacles that result in costly delays in enrollment.

PCI Leadership: This sub-component will be led by **W. H. Wilson Tang, MD.** He has significant clinical research experience as a cardiologist and the clinical research unit director at Cleveland Clinic, leading many changes to bring new services to investigators, including a successful trial of providing access for investigators for EMR-based feasibility and recruitment queries. PCI will be co-led with **Patrick Catalano, MD**, an experienced maternal-fetal medicine physician-researcher involved in many network studies, and a user and director of the clinical research unit at MetroHealth, fully aware of investigators' needs, and **Grace McComsey, MD**, Director of Pediatric Infectious Diseases & Rheumatology at UH Rainbow Babies & Children's Hospital who has successfully conducted single-site and multi-center clinical trials in metabolic and cardiovascular complications of HIV. She is currently the clinical research unit director at University Hospitals, focused on process efficiencies. **Charlotte Bhasin**, CTSC Quality and Efficiency Director, will work closely with *HRC* leadership and *HRC* Research Quality Managers; she has experience facilitating standards across clinical and research sites and facilitating adoption of processes to maximize effectiveness and efficiency of clinical research.

Approach: *Challenges*: Insufficient access to readily available project planning and strong implementation teams with study management skills hinders the advancement of bedside observations becoming realized therapeutic advancements. Researchers are confronted with the following challenges:

- *Accessing Research Resources* – Insufficient knowledge of and fragmented access to personnel, facilities and equipment adversely affect timely launch and completion of projects.
- *Inadequate project planning and insufficient implementation oversight* – Inadequate project planning diminishes the quality of data collected, increases costs, impacting analysis and discovery. Without tightly controlled oversight, studies do not achieve timelines, budgets and milestones; delaying generation of new knowledge.
- *Cumbersome and expensive recruitment processes* – Recruitment inefficiencies, such as manual review of charts or reviewing clinical schedules to find potential candidates, are costly and do not result in timely and sufficient participant accruals.

Availability of Project Management supports Study Completion: Dr. Bhatt, an early-career investigator, was conducting research in the clinical setting, recruiting, consenting, and collecting blood samples; but it was progressing slowly. After 9 months, only 4 of the 30 expected samples were collected. **Project coordination** and **recruitment assistance** by HRC was provided. Enrollment and sample collection rapidly progressed and was completed over the next 7 months. This study has reliable data, moved into data analysis phase and is expected to produce a manuscript soon. We plan to provide critical project management support to young investigators.

We propose to address these challenges through the following aims:

Aim 1: Oversee and assure quality environments (personnel, facilities and equipment) for the conduct of funded research

Innovation: In Aim 1 we will tackle the *Accessing Research Resources* challenge by providing access for funded investigators to utilize quality research facilities, equipment and research staff. **Research Navigators** will facilitate investigator access to resources throughout the CTSC including *Informatics, Research Methods, Translational Endeavors, Community & Collaboration* and recruitment and trial innovation services and processes from across the CTSA through *Network Capacity*. To enhance coordination and communication, Research Navigators are participants in *Hub Research Capacity* Study Start-up Council (see first diagram in Section G. *Network Capacity*). The Study Start-up Councils directly interact with the *Network Capacity* **Project Manager** to assure study coordination efforts across the institutions within the Cleveland CTSA Hub. Along with increased, directed access, Research Navigators assist study-specific staff and provide oversight to assure a quality research environment. The Research Navigators will make optimal use of existing infrastructure, representing participant clinical interactions (e.g., nursing, bionutrition, research subject advocacy, recruitment, study coordination, and laboratory methods). Additionally, Study Start-up Councils will include an IRB facilitator and Contracts facilitator. All will meet weekly to review new project requests. Navigators' expertise guides investigators to resources and allows them to suggest best practice solutions for timely study launch, implementation and completion. Research Navigators oversee a high-quality pool of coordinators, research nurses, bionutritionists and laboratory personnel that can be charged to study budgets

to conduct participant evaluations. A fee-for-service model was adopted by the clinical research units at Cleveland Clinic, MetroHealth, and University Hospitals in July 2015.

Aim 2: Provide project stewardship and oversight for an entire project's lifecycle, from idea conception through study closure and dissemination of results

Innovation: In Aim 2, we tackle the challenge of *inadequate project planning and insufficient implementation oversight* by assigning Project Managers for study co-management using a process adapted by *HRC* from project management paradigms, called the **Research Accelerated Management Process (RAMP)**. The **RAMP Project Manager**, reporting to a **Research Quality Manager**, works closely with investigators to oversee and evaluate the CTSC resources used through the project's lifecycle. Akin to the role of contract research organizations managing large-scale clinical trials, a RAMP Project Manager, embedded within a study team, provides step-by-step study oversight from inception to completion (Fig. 1). Use of this process builds a foundation that promotes quality, efficiency, collaboration, and successful project implementation and study execution. These services are available to eligible investigators, including: CTSC applicants/awardees of Annual Pilot Grants, first-time R01 recipients, KL2 Scholars, local contact PI's of multi-center network studies, and local PI's of CTSA Network studies and others as needs present.

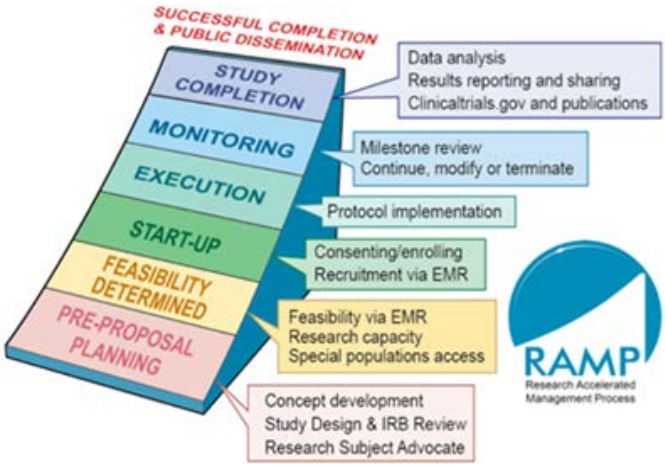


Figure 1: RAMP – Research Accelerated Management Process, is led by Research Quality Managers and executed by Research Navigators, Project Managers and Participant Recruitment Specialists.

Pre-Proposal Planning/Feasibility Determination: A request method (built in REDCap Survey), implemented in January 2015, provides easy access to RAMP Project Management assistance for eligible CTSC investigators. Using this online form, 63% more research service requests for protocol development and/or implementation (containing more accurate information) were received in 2015 compared to 2014. The request triggers an initial consultation between a Project Manager and investigator to assess the viability of an idea, with multidisciplinary input gathered at this early stage of concept and project development. Scientific and regulatory infrastructure approval processes are in place to appropriately vet scientific plans and to aid in appropriate study design. A project's feasibility may be improved by "de-risking" certain elements; investigators have access to best practices and suggestions to remedy projects that may be flawed in science or ethics. These improvements/changes are made and coordinated with input from the other CTSC components to assure projects of the highest quality science and ethics. When the project is determined scientifically sound and logistically feasible, the Project Manager facilitates investigator access to pre-proposal resources to finalize study design and move the proposal forward toward the goal of submission for funding. With the proposal designed, the Project Manager will facilitate development of a study budget that contains appropriate costs for all necessary personnel, supplies and services to successfully complete the project.

Impact of Project Management on Project Start-up: For Phase I/II oncology studies to be competitive for enrollment, rapid study activation is essential. Over 3 months, the Case Comprehensive Cancer Center Seidman Clinical Trials Unit (SCTU) sought to reduce time from scientific approval to activation from over 120 days to fewer than 90. Partnering with the SCTU, the CRU met the SCTU's activation goal using **project management** practices: prioritization, implementation planning to improve start-up communication, weekly status update meetings to track progress of milestones and manage to timelines, and enhanced communication "escalation" strategies to break through activation roadblocks. Using these active management practices, the CRU increased implementation of high acuity protocols by 49% over the past 2 yrs.

Project Start-up: RAMP Project Managers develop action plans for project management oversight to achieve stated project goals, especially for recruitment, retention and completion. Experienced project management guidance and resources are embedded as part of clinical research teams to ensure that project executions are well planned—including scope, resources, quality, risk assessment, timelines and change control processes. Studies benefit from RAMP Project Managers that work closely with research teams and co-manage the project. Together, they evaluate and triage service requests across *HRC* resources (*Informatics, Research Methods, Translational Endeavors, and Community & Collaboration*) and services across the CTSA through *Network Capacity*, and assess and manage needs and requests throughout the project's lifecycle.

Project Execution & Monitoring: To ensure timely and efficient completion of studies, the RAMP Project Manager holds regular meetings with the study team to assess study status relative to stated milestones, timelines and budget. Based on that review, the study continues or is modified to better achieve project goals and assure quality data collection. If a trial is still not enrolling after modifications, it may be ended to prevent wasteful exhaustion of resources.

Study Completion: Upon study completion, the RAMP Project Manager supports orderly closeout of study, data analyses and publication of results, including updates to ClinicalTrials.gov. To ensure timely completion of these tasks, a post-analysis management plan is created and monitored with the PI to track progress of presentations, publications and public dissemination of results.

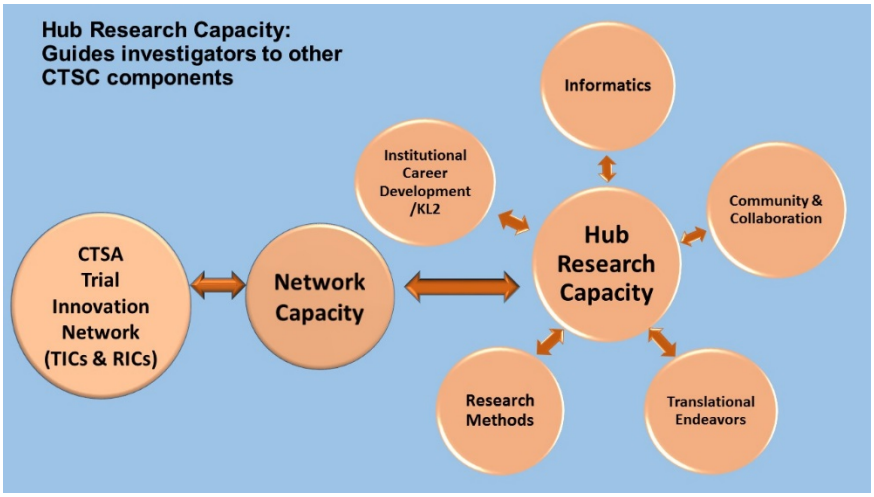
A Successful Recruitment Strategy:
In the Northeast Ohio cohort of the nationally-recognized SPRINT Trial, Dr. Jackson Wright placed experienced study coordinators in 6 urban community-based physician practices to **recruit** from the local community. Five coordinators screened 703 subjects, randomized 442 to the trial and after 4 study years, maintained at least 90% **research subject retention** rate.

Aim 3: Broaden participant recruitment processes with digital tools and strategies to increase efficiencies and decrease cost of recruitment

Personal Health Record-based Approach: Automated review of appointment schedules and participant eligibility identify prospective individuals to receive IRB-approved solicitations through their Personal Health Record (PHR) portal (e.g., MyChart® for Epic® at CC and MH; Touchwork® for Allscripts EHR® at University Hospitals). Individuals will be offered information about ResearchMatch® and websites that feature actively enrolling studies seeking volunteers. Knowledge Program® (KP), a patient-reporting tool (Knowledge Program® [KP]) embedded in the EHR since 2007, can tailor study-specific inclusion/exclusion questions to potential participants, validate information, and provide insights into participant experience at each step of the enrollment process. KP can be deployed beyond Cleveland to anyone with secure web access or an email account and is thus scalable. Prospective participants will also be screened via electronic medical record tools that alert treating physicians to offer their patients opportunities to participate in studies. EMR-based Clinical Trial Alerts (CTA) informs physicians of patients on their schedules meeting specific inclusion criteria and is currently in use at CC.

Registration Opt-in: At the point of care, during patient registration, prospective participants can receive study information (pamphlets, handouts, scripted brief introduction). This technique was piloted to test the feasibility of consenting at the point of registration to opt-in to contribute residual surgical tissues to a biorepository. This opt-in program had a simple brochure in lieu of formal consent forms, and a one-time acknowledgement allowing the Department of Pathology to flag residual samples for research storage and code generation to automatically pull EHR data to a datamart. In the pilot, a total of 1,580 cancer patients were approached at one outpatient registration desk in one month; 81% of patients chose to opt-in. A post-consent survey (n=542) demonstrated understanding of donating specimens for research by 88% of participants.

Interactions between *Hub Research Capacity* and the other components of the Cleveland CTSC: As the first point of access for many investigators, the *Hub Research Capacity (HRC)* component guides investigators towards and helps them manage collaborative interactions with all other aspects of the CTSA Hub. These interactions and referrals across research specialties are key to the success of human studies: *Community & Collaboration* is a Point of Contact to engage special populations in research studies. *Informatics* provides an EMR access point for feasibility assessment of recruitment population planning for age range, gender and ethnic & race diversity; toolsets for capture & analysis of research variables & data. *Research Methods* [Biostatistics, Epidemiology, Research Design (BERD) and Regulatory Knowledge and Support] provides appropriateness of study design and power calculations. Translational Workforce Development (TWD): uses *HRC* for controlled research environments to educate and support young investigators, KL2 scholars and new translational investigators.



EVALUATION METRICS: INTEGRATING SPECIAL POPULATIONS			
Aim Area	**Measurable Objectives**	**Implementation strategies (Milestones)**	**Evidence of Success/Metrics**
Aim 1: Proactively identify recruitment needs across the lifespan and special populations, by establishing Point Persons to provide investigators better access to under-represented populations to broaden applicability of research results	Establish Participant Recruitment Specialist processes (PRS)	• Protocol review process & best practices (Redcap Survey process, Diversity Recruitment Checklist) • Modify study designs or recruitment plan	• % studies using PRS for planning & assistance with recruitment
	Establish special populations system (points persons & new processes)	• Build relationships w/ point persons • Provide specific consultations • Foster collaborations • Identify additional, unique opportunities	• % grant applications submitted with special population recruitment plans
Aim 2: Expand Health Disparities Consult Service to include clinical research recruitment plans to address the challenges to participation that affect populations with health disparities	Increase access to populations with health disparities	• Consultations with researchers to plan recruitment and retention of special populations	• % of recruitment consults that led to proposals including recruitment plans for populations with health disparities
Aim 3: Facilitate investigator training and access to existing, underutilized recruitment tools to better integrate special populations and achieve full enrollment.	Increase use of tools to access special populations	• Protocol review/provide recruitment plan • Expanded access to tools: Knowledge Program, ResearchMatch (RM) • Train study teams in use of tools • Expand sign-up campaigns strategically launched to specific populations	• % Recruitment plans that include recruitment tools • Number of individuals educated in tool use • ↑ % RM sign-ups by special populations • Number of studies that achieve full enrollment • Number of studies that meet enrollment timelines

EVALUATION METRICS: PARTICIPANT AND CLINICAL INTERACTIONS			
Aim Area	**Measurable Objectives**	**Implementation strategies (Milestones)**	**Evidence of Success/Metrics**
Aim 1: Provide quality *HRC* facilities/ staffing	Facilitate access to resources, guide and assist study-specific staff	• Multidisciplinary review of *HRC* studies • Review all studies using *HRC* resources • Access to skilled pool of personnel	• Number of studies assisted by *HRC*
Aim 2: Project stewardship through entire process	Study co-management through the Research Acceleration Management Partnership (RAMP)	• RAMP project development; recruitment plans; retention/completion plan; dedicated project manager; workflows; milestones & budget; quality & data monitoring; closeout, data analysis, results reporting; track dissemination • Annual Pilots awardees use RAMP	• % meeting recruitment/retention/ completion goals • % Pilots completing • % studies that adhere to planned timeline from study closure to submission of manuscript for publication/ presentation
Aim 3: Broaden participant recruitment processes	Increase identification & solicitation of eligible study participants	• Personal Health Record-based Approach • Direct KP-based solicitation/Clinical Trials Alert • Registration Opt-in Approach	• % patients solicited who enroll via PHR • % patients solicited who opt-in via EHR

In summary, *Hub Research Capacity* with its focus on **Integrating Special Populations** and **Participant and Clinical Interactions** will facilitate the appropriateness of specific study designs, steps to ensure the timely assessment of feasibility, development of realistic recruitment plans and goals, tracking of enrollment, follow-up, submission of high quality data, careful data monitoring, closure of studies that do not meet goals, orderly closeout, publication and dissemination of results. As a result of more efficient implementation processes, more studies will come to completion, and with lower overall costs.

G. Network Capacity

SPECIFIC AIMS

The goal of the *Network Capacity (NC)* component is to develop a local **Trial Innovation Unit (TIU)** and a local **Recruitment Innovation Unit (RIU),** while delineating a framework for the interaction of local structures with their "national" counterparts, including NCATS CTSA Trial Innovation Network (TIN). Our specific aims are designed to facilitate participation in multisite clinical trials and increase the speed at which clinical trials are conducted. We will use our experience participating in other clinical trial networks such as NeuroNEXT, AsthmaNet, the Severe Asthma Research Program, the Neonatal Research Network, and the Cystic Fibrosis Therapeutics Development Network to extend processes and joint standard operating procedures (SOPs) to clinical trials in all disease areas at our partner institutions.

The *NC* component consists of two subcomponents: the TIU and the RIU. The Cleveland CTSA will coordinate services that facilitate clinical trial implementation and conduct across the Cleveland CTSC hospitals, while interfacing with other CTSA Hubs to speed the delivery of novel therapeutics to patients. We will achieve this by capitalizing on solid support from our individual institutional administrative leadership, and building on our long experience with streamlining regulatory aspects of study conduct (e.g. Reliant IRB, centralized contracting), interfacing with the electronic health records and using digital media for successful recruitment for multi-site clinical trials while streamlining and solidifying processes of collaboration with other components within our CTSC to ensure adequate outreach to the community of Special Populations. *NC* will share personnel with the *Hub Research Capacity* because neither of these components require 1.0 FTEs. Personnel at each institution will work on both *Network Capacity* and *Hub Research Capacity* projects. The *NC* team will also leverage *the Hub Research Capacity* at each institution as institutional thought leaders in clinical research. *NC* will coordinate with *Hub Research Capacity*, Regulatory, and Community Outreach at each of our institutions to develop a **"Study Start-up Council"** to further improve study implementation and conduct, and facilitate communication and the execution of joint SOPs developed by the national TICs and RICs at all CTSC affiliated hospitals while adapting to "local context".

Specific Aim 1: To establish a TIU that will collaborate with other CTSA Hubs and national TICs to facilitate study implementation through the expansion of coordinated services and ensuring the adherence to joint SOPs. We specifically propose the following sub-aims:
Aim 1a: Create a directory of skilled disease experts willing to serve as site PIs of multicenter clinical trials that will be used by the point person (Research Navigator) at each hospital so that we are able to promptly identify a site PI when a clinical trial opportunity presents
Aim 1b: To leverage current processes and to develop new processes that expedite budget and contract negotiations
Aim 1c: To track, analyze, and continuously improve site performance of multisite (CTSA) clinical trials in real time at each participating CTSC hospital so that impediments to study completion will be resolved quickly.

Specific Aim 2: To establish a RIU and collaborate with other CTSA Hubs and the national RIC to enhance patient recruitment to multi-site clinical trials conducted at our Hub. Our proposed RIU will increase patient and investigator engagement, optimize the use of electronic health records (EHR) to identify potential study subjects, and optimize existing infrastructure to assist investigators in developing and tracking recruitment strategies. We specifically propose the following sub-aims:
Aim 2a: Enhance an existing health-education web-based patient interface (NetWellness) by extending its content to include educational materials on the research process and information on available clinical trials rendered in lay language. This will improve public awareness and population engagement with clinical research.
Aim 2b: Build on existing systems of secure survey delivery to allow potential subjects to: i) enter clinical information generating a patient registry that can help determine their eligibility for trials, and ii) to facilitate the delivery of study updates and available results to subjects who complete study participation, ensuring their ongoing engagement in clinical research and nurturing their advocacy of research.
Aim 2c: To leverage and enhance existing electronic systems that interface with the CTSC hospitals' EHR systems generating an innovative mechanism for feasibility assessments and recruitment.

Component Lead: This component will be led by **James Chmiel, MD, MPH,** Director of the CF Therapeutics Development Center at CWRU and UH and by **Lara Jehi, MD**, Associate Director of the Clinical Research Unit and Research Director of the Epilepsy Center at the Cleveland Clinic. **Dr. Chmiel will be our TIU Lead and *Liaison to Trial Innovation Centers (LTICs),* and Dr. Jehi will be our RIU Lead and *Liaison to Recruitment Innovation Centers (LRICs*).** Both Drs. Chmiel and Jehi will serve as Co-Medical Directors in the newly developed NCATS CTSA Trial Innovative Network.

NC: Trial Innovation Network Hub Liaison Team

Goals: To establish a TIU and collaborate with the national TICs to improve study implementation and conduct and increase investigator engagement in multi-site trials and To establish a RIU and collaborate with the national RIC to increase patient and investigator engagement, optimize the use of EHR and communications technology to identify potential study subjects, and assist investigators in developing and tracking recruitment strategies. The Cleveland CTSA will expand upon current processes present at our site, including the use of reliant IRBs and master CDAs, clinical trial research agreements, and budget templates that were used by the Ohio Clinical Trials Collaborative (OCTC), which included five universities and 14 hospital systems in Ohio (including all three Ohio CTSA Hubs). In addition, the investigators at our institutions have experience participating in **many clinical trial networks** such as NeuroNEXT, the Cystic Fibrosis Therapeutics Development Network, AsthmaNet, the Inner City Asthma Consortium, the Severe Asthma Research Program, Neonatal Research Network, and the Heart Failure Network, most of which are supported by the NIH, amongst others. Our investigators, who often have been founding members of these networks, have served as lead PIs on many multisite site studies, and are willing to share SOPs and their experience with others. The breadth of clinical research conducted by the CTSC partners is evident in Table 1, which due to space limitations, only shows a partial listing of Phase III studies conducted. Our investigators are willing to serve as institutional PIs for trials, and are willing to help educate other specialists on how to serve as institutional PIs in multi-site clinical trials. We will use all the resources detailed below to develop a national network capacity and improve multi-site clinical trial readiness.

Program Leadership: The *Network Capacity (NC)* Component will consist of Liaisons to the TICs and RIC who will also serve as Co-Medical Directors of the TIN Hub Liaison Team (**James F. Chmiel, MD, M.P.H.**, and **Laura Jehi, M.D.**), and a full-time Project Manager (**Ms. Noreen Roman, MBA**). Dr. Chmiel, of University Hospitals Cleveland Medical Center, will focus on clinical trial implementation and conduct, and Dr. Jehi, of the Cleveland Clinic, will focus on recruitment. The *NC* will develop in coordination with *Hub Research Capacity* a local "**Study Start Up Council**" (SSC) at each institution consisting of a Research Navigator, who will review and help resolve the regulatory and administrative hurdles to study initiation, an IRB Facilitator, who will expedite IRB documents through the reliant IRB, a Contracts Facilitator, who will facilitate the use of standard budget templates and master contracts to speed up study start-up, Informaticists (IT experts), who will help navigate diverse computer systems, and a Participant Recruitment Specialist, who will adapt the CTSC's resources to the needs of the individual study. To streamline the workflow and avoid overlap between the *Network* and other Hub Components, Drs. Chmiel and Jehi will work with the Project Manager to communicate with the SSC members at the three institutions, while each Site *Hub Research Capacity* Leader provides direct supervision of individuals because of their familiarity with institutional policies.

The Project Manager will be responsible for the day to day management of the *NC* Component/TIN Hub Liaison Team, and will have practical experience managing clinical trials and understanding the business aspects of conducting clinical trials. The Project Manager will work with each site's Research Navigator and their local investigative teams to oversee training of research staff, develop processes to improve clinical trial conduct, and ensure deployment and adherence of national joint SOPs at the sites. The Research Navigators will be employees of each institution's research office and serve as the bridge between the local investigators and *NC*. The *NC* team will meet weekly to discuss all aspects of clinical trial implementation, conduct, and recruitment at the local institutions. Each SSC will meet at least once monthly to ensure that SOPs and other initiatives adapt to and are compliant with local institutional policies. SSC members will be accessible points of contact for local investigators and sponsors seeking help with study initiation and development of recruitment strategies. SSC members also will work with *NC* to review and help resolve the regulatory and administrative hurdles, adapt the CTSC's resources to the needs of individual studies, refine study protocols and informed consent documents, and coordinate post-study completion tasks.

Research Strategy/Approach: In each aim, we address specific challenges currently hindering study conduct and recruitment. We build upon current successful programs by adding new programs while maintaining a conscious effort to integrate with other CTSA components.

Aim 1a: To create a directory of skilled disease experts willing to serve as site PIs of multicenter trials.

Challenges: It is often difficult for sponsors to identify well-established investigators willing to participate in some clinical trials because of time demands or lack of interest. This is particularly true for large Phase III studies in which investigators will not receive significant academic credit in the form of grants and first-authored papers. *Expansion of Current Programs:* The TIU/Hub Liaison Team will expand upon the methods we currently utilize to identify potential investigators: Pure Experts (formerly Sci-Val Experts) and the CTSC Research Concierge. The *NC*/Hub Liaison Team will **create a directory of potential investigators** willing and able to participate in

clinical trials within each disease area at all of the Cleveland CTSC hospitals. Increasing enthusiasm of investigators to participate in large Phase III studies will be a priority of the *NC* Team. We will meet with Department Chairs to create a directory of willing investigators able to participate in clinical trials and devise an **incentive plan for garnering institutional participation** within each department to engage in CTSA-supported clinical trials. We will also establish bidirectional collaboration with mutual support for overlapping processes with both *Hub Research Capacity* and *Community and Collaboration*. While clinical research is often considered the domain of specialists, many clinical trials focus on interventions geared towards common diseases primarily cared for by community physicians. The conduct of these studies must not disrupt a busy clinical practice. To **increase the enthusiasm of primary care providers for clinical research participation**, the Cleveland CTSA will support busy practitioners by sending research coordinators to individual practitioners' offices and study participants' homes and employing satellite clinical research offices.

Aim 1b: To expedite budget and contract negotiations.

Challenges: The greatest barriers to timely study initiation are prolonged budget and contract negotiations, which often take several months. A delay in study initiation will delay study completion, and ultimately slow the time in which therapies are available to patients. *Expansion of Current Programs:* The Cleveland CTSA has many tools at its disposal that will shorten budget and contract negotiations. **All of our institutions have Master Service agreements with multiple pharmaceutical sponsors.** In addition, we will leverage several tools created by the OCTC for this initiative. These tools will allow us to sign agreements and represent the entire Cleveland CTSA, thus shortening budget and contract negotiation time. Each SSC will employ a Budgets and Contract Facilitator who will develop a paradigm for writing an appropriate budget at their institutions. *NC* will collaborate with *Research Methods* (Regulatory Knowledge and Support*)* for assistance with this process. We will meet at least monthly with Regulatory Knowledge leaders to review the successes and challenges and to develop solutions to problems regarding study implementation and conduct.

Aim 1c: To track, analyze, and continuously improve site performance of multisite (CTSA) clinical trials in real time at each participating CTSC hospital so that impediments to study completion will be resolved quickly.

Challenges: Measuring performance is critical in determining whether our processes and SOPs have shortened the time to study completion. To achieve this, we will track trial activation, enrollment, compliance, retention, and completion of multisite CTSA trials with a view to making real-time interventions to improve performance. Currently, we have data on some clinical trials (Table 1), particularly those that are part of disease networks in which there is a coordinating center. However, we have not collected these data on every clinical study conducted at all of our CTSA institutions. One of our major objectives is to collect metrics on all clinical trials so that we can institute a process of continuous quality improvement. *Expansion of Current Programs:* Our investigators participate in disease networks that allow us to collect data related to study performance. We use these data to design quality improvement projects. **We will expand this quality improvement program across all studies.** Dr. Chmiel is highly qualified to oversee these clinical trial quality improvement projects. He has been a PI in 3 NIH networks and currently is the PI at the Cystic Fibrosis Foundation Therapeutic Development Center located at CWRU. Dr. Chmiel received his quality improvement training while participating in 3 Learning and Leadership Collaboratives organized by the Cystic Fibrosis Foundation and served as a coach in the CFF Therapeutic Development Network's first electronic quality improvement in clinical research (eQUIP-CR) program. We will work closely with the evaluation group of the *Administrative Core* (**Clara Pelfrey**) and the *Informatics group* to broaden our ability to collect and analyze performance data for all clinical trials. We will use this information to **establish a CQI program** to address barriers to timely study completion in real time and allow us to compare the performance of our hospitals to national standards. We will adhere to joint operating procedures and enter our data into a national registry in a timely fashion. We will also participate in any national quality improvement projects. We have arranged collaborations with the University of Washington CTSA to share best practices (see letter of support), and will participate in CTSA network QI projects.

Aim 2a: To enhance an existing health-education web-based patient interface.

Challenges: For successful recruitment, a study should address a need that is important to patients, and patients should feel engaged in its conduct and success. A recent patient poll identified lack of awareness of clinical trial opportunities (53%), lack of trust in the clinical trial conduct (53%) and a perception that clinical research is too risky (51%) as the top obstacles to participation in clinical trials (researchamerica.org/2013clinicaltrialspoll). Current web-based resources such as ClinicalTrials.gov have thus far proved insufficient to stimulate participation in trials. *Expansion of Current Programs:* Beyond **traditional informational tools** (study flyers, meetings, advertisements), the Cleveland CTSC has built **key public partnerships**. For example, a public

broadcasting partnership with Ideastream, Ohio's largest public broadcasting group (National Public Radio), led to a national three-part PBS documentary in the spring 2015. The role of clinical trials in advancing cancer care was prominent, and a new cancer clinical trials resource developed by CWRU researchers was featured: this video-based program, called Preparatory Education About Clinical Trials (PRE-ACT) reduced barriers to trial participation, and was made available online through Cancer.Net from the American Society of Clinical Oncology. This and other examples are featured on **NetWellness** website. NetWellness, a partnership between CWRU, Ohio State, and University of Cincinnati, provides health information to the public with more than 67,500 visitor questions answered by faculty experts since 1995, offering an **established digital platform** for communication with patients. *New Programs:* we will expand the NetWellness content to educational material related to the general process of clinical research with lay-language description of clinical trials offered in our CTSC. We will use the model of University Hospitals Seidman Cancer Center, where input from patients, caregivers, clinicians, and researchers guided the creation of a **searchable, mobile friendly web resource** responsive to phone tablet and web platforms and that improved recruitment to cancer clinical trials conducted at CWRU. We intend to continuously engage previous trial participants and their families through different stages of the website development and beyond to facilitate trial engagement. To create a sustainable content generation structure, the Participant Recruitment Specialist within our Study Start up Council will assist investigators in developing a **lay language study description**. We will also enhance our existing **modules on "Recruitment Strategies"** and offer these to study teams so that they develop an independent capability to generate such content. Links to NetWellness will be made available on all institutional websites of our CTSA hospitals, promoting its visibility as a **health and research education website**. Patients can learn about clinical trial opportunities in understandable language and contact the study team or their physician to express interest. Our Study Start-Up Council will coordinate with our *Community and Collaboration* component to trigger referrals to their **Special Populations and Dissemination Consult Service** as needed, growing **non-digital outreach methods** for minorities and the underprivileged.

Aim 2b: To build on existing systems to generate a patient registry and ensure ongoing engagement of study participants.

Challenges: A variety of factors impact potential participation in clinical trials rendering it a challenge to estimate without well-designed and relevant feasibility assessment tools. Not all people listed in disease-specific registries are equally interested in clinical trials; some may prefer to avoid all trials; some may be ineligible for trials in which they would like to participate; some would like as much information as possible. Unless participants have a positive experience related to clinical trial participation, they may be reluctant to seek to enroll in a subsequent trial and may discourage others from doing so, as well. Hence, prompt and accurate assessment of the practicality and feasibility of a study, paired with a sustained pool of meaningfully engaged potential study participants is critical. *Expansion of Current Programs:* Multiple **disease-specific registries** currently exist within each of our institutions, but are not easily accessible to investigators at all CTSC hospitals, so their ability to facilitate multi-institution feasibility assessments is limited. Similarly, we judge that unilateral "information shoving" at patients is an ineffective recruitment strategy: we piloted a web-based program designed to provide simplified descriptions of open clinical trials and contact information to individuals with specific diseases. Despite over 5,000 website views and 102 calls, there was no increase in enrollment for reasons ranging from not meeting study criteria to not being interested. *New Programs:* To achieve enrollment goals, we will devote our resources to develop strong, positive relationships with potential study enrollees enriched by screening out ineligible, disinterested, and risk-averse individuals and concentrating on providing a user-friendly, informative, and supportive environment for trial-eligible, interested, and cooperative participants. Research Match can include a link to an IRB-approved pre-screening REDCap survey that will allow deeper probing of study eligibility reducing the rate of "false positive" screens. 182 researchers in the Cleveland CTSC used ResearchMatch within the past 5 years. We intend to **expand** this option by informing patients about **ResearchMatch** in the specialty offices of our CTSC institutions and encouraging them to sign-up. We will also expand the **Knowledge Program (KP),** a Health IT system developed by the Cleveland Clinic in 2007, housing patient reported outcome data and clinical information seamlessly derived from the EHR, and with a functionality **("Time Based Questionnaires**") allowing the timed delivery of surveys to patients via their email. We will build a link URL from NetWellness to the TBQ, allowing patients to complete detailed pre-screening surveys. Patients will have the option to repeat this prescreening in the future, thus maintaining an updated an accurate pool of potential study subjects. This improved registry mechanism (ResearchMatch and KP), paired with optimized EHR-based queries (Aim 2c) will provide better feasibility assessments. We will deliver "Thank you" messages and "Study News" to study subjects through the TBQ functionality to maintain engagement.

Aim 2c: to leverage and enhance existing interfaces with EHR systems for feasibility assessments and recruitment.

Challenges: The EHR is an underutilized resource for clinical research. *Expansion of Current Programs:* Multiple EHR search tools permit our team to rapidly obtain access precise numbers of study-eligible individuals from a pool of several million patients in our health systems. In the MetroHealth system, Dr. Kaelber and his team use **Explorys** to quickly search through the EHRs of over 1 million unique patients in their EHR based on discrete demographic and clinical data. An example is a recent prospective IRB-approved study of chronic arm/hand hemiplegia that was under-recruiting. Using Explorys, it took about 10 minutes to convert study inclusion and exclusion criteria (age range, diagnoses, still living, seen at MH in the last year) into discrete searchable data elements which then generated 930 eligible patients in less than 1 second. Systems like the KP and Explorys are already used in our CTSC to interface with the EHR and provide a ready resource to deliver prompt feasibility assessments for sponsors considering our CTSC sites. Through recent pilot studies, the KP and other tools available through our *Informatics* component have been used to trigger electronic alerts to treating physician in the context of outpatient clinic visits based on pre-specified patient criteria and in pre-specified clinical contexts, and to email study personnel when EHR data suggest a patient for potential eligibility in a clinical trial. These direct tools of communication allow subject identification at the point of care, so physicians inform potentially eligible patients about clinical trial opportunities and study coordinators have a chance to approach patients in a timely fashion. *New Programs:* We will dedicate more resources for Explorys and the KP, to both streamline their use and train research coordinators to use these tools. The Participant Recruitment Specialist will bridge between the study team and *Informatics* staff to create the EHR queries based on study criteria, translating the "medical language" of a protocol into "informatics language". With long experience with EHR interfacing and clinical trials, we have a precious pool of individuals with this unique skill set. The Recruitment Specialist and the Participant Research Navigator at each institution will work within each SSC to identify the alert method (paging, emailing, or pop-up alerts during visits) best suited for the study, departmental policies, and study resources.

Evaluation Metrics: Network Capacity		
Objectives	**Milestones**	**Tracking metrics***
AIM 1: Establish a multi-faceted Trial Innovation Unit (TIU)		
1a: Rapid identification of trial site-PI	• Hire research manager at all 3 medical institutions • Create directory of trial experts • Develop incentive plan for investigators to increase engagement	• ↓ time from receipt of protocol to IRB approval • ↓ time from receipt of protocol to first subject visit • ↓ time from receipt of protocol to first subject first visit • ↑ # of multisite clinical trials placed at Cleveland CTSA hospitals • ↑ use of Experts directory to rapidly assign clinical trials
1b: Shorten time to completion of budget and contract negotiations	Coordinate all preliminary processes for maximum efficiency: • Expedite budget preparation • Expedite contract negotiations • Create Study Start-up Council	• ↑ % trials w/ 1st subject w/in 90 days of contract rec'd • ↑ % roadblocks successfully addressed • ↓ % trials which fail to enroll any study subjects • Track dates for multisite trials (reduce time): contract received; contract executed; protocol received; sub-contract started; site activation sponsor; IRB approval; 1st subject visit
1c: Conduct CQI for all multi-site clinical trials	• Develop trial data collection system • Collect data on performance • Analyze performance metrics • Develop QI initiatives:under-performing sites	• # QI initiatives being conducted at Cleveland CTSA sites • % studies meeting timeline goals for subject enrollment • % subjects retained in a study • ↑ sites meeting targets: performance, enrollment, retention, completion
AIM 2. Establish a multi-faceted Recruitment Innovation Unit (RIU)		
2a: Enhance NetWellness to increase # eligible trial participants	• Mobile friendly web resource • Lay language study descriptions • Promote & advertise NetWellness • Develop non-digital outreach methods for minorities & underprivileged pts	• ↑ % enrollment via NetWellness • % ↑ linked to Netwellness • ↑ % URM enrolled vs. Targeted enrollment • ↑ **#** CTSA sites using Netwellness
2b: Develop patient registry for eligibility and study update delivery	• Build a study subject registry • Design surveys to obtain patient data for registry • Provide study updates/results to participants • Expand information distribution: Research Match	• %↑ registrants & ResearchMatch registrants • Feedback from subjects • Completion rate of timed surveys • Time to 1st patient enrolled • Drop out rates w/wo patient engagement • Trials meet yearly enrollment goals
2c: Expand EHR systems for feasibility assessments & recruitment	• Develop Knowledge Program (KP) to alert physician re: eligibility criteria • ↑ KP email notification in more departments • Recruitment Specialist & Informatics create KP/ Explorys queries for studies	• ↑# alerts to physicians re: eligibility • ↑# departments using KP • ↑**#** target population identified • ↑# recruitments/ EHR query • ↑# recruitments/ EHR alert

*Data sources- existing:	*Data sources- existing:	*Data sources- proposed:
IRB databases: CC, MH, UH	Health IT systems (Explorys, KP)	Clinical trial experts directory
eQUIP-CR: electronic QI program	EHR (EpicCare)	Phase III Clinical Trial database
Netwellness	Investigator Research Profiles (SciVal / Pure Experts)	Study Subject Registry
Survey systems (Redcap, KP-TBQ)		QI system

Table 1: Timeline table of NIH-defined Phase III trials with site activation within the Cleveland CTSC institutions from January to June 2015. Due to space limitations, the studies below are a representative sample from 112 eligible protocols illustrating several key points that guided our planning for areas of strength and opportunities for improvement in our *Network Capacity* proposal: 1) most of our studies (56%) meet or exceed recruitment goals (shaded rows); 2) gaps predominantly exist in our ability to track study performance between regulatory endpoints (contract execution and IRB approval) and first patient enrolled; 3) study conduct and recruitment challenges are seen in all specialties. UH=University Hospitals; CC= Cleveland Clinic; N/A= not available.

Protocol Title/ Description	Disease area	Contract receipt to execution (days)	Protocol receipt → IRB approval (days)	Subcontract executed → patient first visit (days)	IRB approval → patient first visit (days)	Planned monthly enrollment	Actual enrollment at the Hub	Institution
A Multicenter Phase 3 Randomized, Open-Label Study of Bosutinib versus Imatinib in Adult Patients with Newly Diagnosed Chronic Phase CML	Cancer	184	192	N/A	N/A	0.33	0	UH
Randomized Trial to Prevent Vascular Events in HIV – REPRIEVE	Cardiology	41	62	48	84	0.83	1	UH
A Phase 3, Multicenter, Open-label, Randomized Study of SGI-110 versus Treatment Choice in Adults with Previously Untreated AML Who Are Not Considered Candidates for Intensive Remission Induction Chemotherapy	Cancer	146	141	N/A	N/A	0.33	0	UH
A Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma	Cancer	101	7	N/A	N/A	0.5	0	UH
Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source	Neurology	94	97	144	141	1	0.2	UH
A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study To Evaluate the Safety and Efficacy of Pyridorin™ (pyridoxamine dihydrochloride) in Subjects With Nephropathy Due to Type 2 Diabetes (PIONEER)	Nephrology	184	196	49	93	1	0.2	UH
Risk-Stratified Randomized Phase III Testing of Blinatumomab in First Relapse of Childhood B-Lymphoblastic Leukemia	Cancer	18	78	113	223	1	1	UH
A Phase III RCT of Pembrolizumab (MK-3475) versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer	Urology/cancer	17	48	89	207	1.5	4	UH
A single-arm, open-label, multicenter Phase 3 study of the contraceptive efficacy, safety and tolerability of the AG200-15 transdermal contraceptive delivery system	OB/GYN	157	151	35	44	5	1	UH
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Subcutaneously Administered Bremelanotide in Premenopausal Women with Hypoactive Sexual Desire Disorder (HSDD) (with or without Decreased Arousal)	OB/GYN	90	65	55	69	3.5	4	UH
Phase 3 Study of IV to Oral 6-Day Tedizolid Phosphate Compared with 10-Day Comparator in Subjects 12 to <18 Years with cSSTI	Infectious disease (ID)	72	99	N/A	N/A	0.1	0	UH
A Randomized, Double-Blind, Multinational Study to Prevent Major Vascular Events with Ticagrelor Compared to Aspirin in Patients with Acute Ischaemic Stroke or TIA	Neurology	178	47	N/A	N/A	1	0	UH
A Long-Term, Open-Label Extension Study Of Tofacitinib For Psoriatic Arthritis	Rheumatology	133	81	221	255	1	2	UH
Prospective, Open-Label Study Of Andexanet Alfa In Patients Receiving A Factor Xa Inhibitor Who Have Acute Major Bleeding	Hematology	101	11	240	309	1	0.5	UH
World-wide Randomized Antibiotic EnveloPe Infection PrevenTion Trial (WRAP-IT)	ID	112	8	34	118	2	3	UH
A 6-week, Randomized, Double-blind, Multicenter, Placebo-controlled, Parallel-group Efficacy and Safety Study of Dasotraline versus Placebo in Subjects 6 to 12 Years of Age with Attention Deficit Hyperactivity Disorder (ADHD)	Pediatrics	154	71	59	90	3	3	UH
A Phase 3 Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ALN-TTRSC in Patients with Transthyretin Mediated Familial Amyloidotic Cardiomyopathy	Cardiology	49	6	N/A	N/A	0.25	0	UH
		41	60	17	26	0.25	0.25	CC
Clinical Evaluation of the Xpert® HCV VL Assay	GI	71	33	34	76	1	1	UH
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661+Ivacaftor in Subjects Aged 12 Yrs and Older With Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation, and a Second Allele With a CFTR Mutation Predicted to Have Residual Function	Pulmonary	168	49	153	120	0.8	0.9	UH

A Phase 3, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation	Pulmonary	30	36	84	84	1.25	1.75	UH
An Open-Label Study Of Dupilumab In Patients With Atopic Dermatitis	Derm	63	133	42	55	1	3	UH
A Randomized, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Ulipristal Acetate for the Intermittent Treatment of Abnormal Uterine Bleeding Associated with Leiomyomas	OB/GYN	80	71	35	63	2	1	UH
A Randomized, Controlled, Parallel, Multicenter Study Assessing Perfusion Outcomes with PINPOINT® Near Infrared Fluorescence Imaging in Low Anterior Resection	GI	60	41	40	20	2	1.5	CC
Phase III Trial to Confirm the Anti-anginal Effect of T89 in Patients with Stable Angina	Cardiology	28	93	10	24	2.5	2	CC
Bioflow-V: A Prospective Randomized Multicenter Study to Assess the Safety and Effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System in the Treatment of Subjects With Up to Three De Novo or Restenotic Coronary Artery Lesions-V	Cardiology	14	56			0.33	0	CC
A 12-Month, Dose-Level Blinded Study Investigating the Safety and Efficacy of CVT 301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena)	Neurology	20	95	40	14	1	1	CC
A Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Two Dose Strengths of Dalfampridine Extended Release Tablets for Treatment of Stable Walking Deficits in Post-Ischemic Stroke	Neurology	46	124	97	146	1	1	CC
A Phase 3, Multi-Center, Randomized, Double-blind, Double-dummy, Active Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients (SUNBEAM)	Neurology	62	169	44	44	1.5	1	CC
GSI 3Z14 - A Phase 3, Randomized Study To Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib	Cancer	13	302	121	168	0.5	0.3	CC
GENE1815 A Phase III, Open-Label, Randomized Study of MPDL3280A (Anti-PD-L1 Antibody) In Combination with Bevacizumab Versus Sunitinib In Patients With Untreated Advanced Renal Cell Carcinoma	Cancer	57	71	38	128	0.83	0.83	CC
MRK1814 A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer	Cancer	24	136	151	151	0.5	0.75	CC
A Multicenter, Open-Label Trial of Intravenous Golimumab, a Human Anti-TNFa Antibody, in Pediatric Subjects with Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy.	Pediatrics	51	N/A	N/A	N/A	2	0	CC
A 26-week Open Label, Randomised, Two-armed, Parallel Group, Multi-Center Trial Investigating Efficacy and Safety of Insulin Detemir Versus Insulin Neutral Protamine Hagedorn in Combination with Metformin and Diet/Exercise on Glycaemic Control in Children and Adolescents with Type 2 Diabetes Insufficiently Controlled on Metformin +/- Other Oral Antidiabetic Drug(s) +/- Basal Insulin	Pediatrics	15	N/A	N/A	N/A	2	0	CC
A Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-0431A XR (A Fixed-Dose Combination Tablet of Sitagliptin and Extended-Release Metformin) in Pediatric Subjects with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Monotherapy	Pediatrics	42	N/A	N/A	N/A	2	0	CC
Efficacy, Immunogenicity, and Safety Study of Clostridium difficile Toxoid Vaccine in Subjects at Risk for C. difficile Infection (14-25D)	Infectious disease	N/A	N/A	N/A	150	9	9	MHS
Amgen 20130207 (15-08DL)		N/A	N/A	N/A	210	N/A	2	MHS

I. Institutional Career Development Core: Mentored Career Development Award (KL2)

BACKGROUND and AIMS

A cadre of experts are needed to address the lack of optimal management strategies for hundreds of diseases and conditions and for special approaches across the entire population, including special and vulnerable populations and the age spectrum. To help provide the requisite expertise, the CTSC seeks to support the development of secure, confident, and expert investigators who will be enabled to provide innovative solutions to these unmet health needs. To support the development of such investigators, we established and deeply entrenched a culture of interdisciplinary collaboration at all levels during the first two cycles of our program. As we move forward, we seek support for an educational curriculum designed to meet the special needs of emerging, talented investigators across all disciplines in high standards of research, including outstanding biomedical statistical and research design programs, cutting edge informatics, collaborative investigation, detailed knowledge of novel methodologies and management of big data, cultural sophistication required to identify and pursue creative solutions to unmet health needs, and expertise in the fine art of negotiating the regulatory pathways and the dissemination of best practices so that results of high quality research are rapidly and economically disseminated to the public. We aim to ensure success by proposing an innovative program that adapts to the individual needs of each scholar and builds upon and improves on our existing highly successful program to address unmet educational and career development needs of clinical research scholars of all professions in the rapidly evolving field of clinical and translational science.

Abbreviations

MCDA: Mentored Career Development Award (This KL2 program)
CTSTP: Clinical and Translational Scientist Training Program (TL1 training program)
C/T: clinical/translational
CWRU: Case Western Reserve University
CTSC: Clinical and Translational Science Collaborative (CWRU CTSA program)
SOM: School of Medicine
SOE: School of Engineering
SON: Frances Payne Bolton School of Nursing
CCF: Cleveland Clinic Foundation
UHCMC: University Hospitals Case Medical Center
VAMC: Louis Stokes Cleveland Veteran's Administration Medical Center
MHMC: MetroHealth Medical Center
CCLCM: a five-year research-intensive MD program provided by Cleveland Clinic Lerner College of Medicine of CWRU
TWD: translational workforce development
OTWD: Office of Translational Workforce Development (section D, CTSC application)
RCR: responsible conduct of research
TGE: training grant eligible
CRTTT: Clinical Research Team Training Taskforce
URM: underrepresented minority
CRSP: Clinical Research Scholars Program

Tables include NIH format Tables 2 and 8; additional tables with letter designations are embedded in the text. Tables report prior period data through June 30, 2015 or current status as of May 2017.

We intend to address unmet needs by:

1) Educating leaders in multidisciplinary clinical and translational research.
2) Introducing clinical research education earlier in the life cycle of scholars from diverse disciplines (nursing, bioinformatics, social work, engineering, pharmacology, psychology, etc.).
3) Tailoring programs to the preferences, special interests, research plans, strengths, and weaknesses of each scholar with appropriate modifications, as required, for each discipline.
4) Setting the standards and developing innovative approaches to C/T career development.

Our program builds on:

1) Lessons learned from our own experience in running a powerful KL2 program with a high rate of successful transitioning of scholars to independent academic careers at an early age, high rate of collaboration across disciplines and institutions, a novel mentoring program with a proven and published career planning tool,[1] and an overall seamless inter-institutional collaboration. Examples: the **two-mentor approach, experiential multidisciplinary education,** exceptional exposure to cross the spectrum (T1–T4) training, and early introduction to multiple communities and stakeholders.
2) Proven strategies from published national studies on mentorship[2-18] and approaches recommended by these studies to attract and retain promising young people, especially ethnic minorities, into C/T research. Examples include selecting scholars with focus and readiness to embrace the whole spectrum of C/T research and help them expand their competency so they can make important contributions to addressing unmet health needs**.** This requires the utilization of **mentoring best practices** and **mentor development**.

3) Collaboration with other CTSA-Hub KL2 sites (like the Ohio Collaborative and others) to facilitate the ability to learn from each other, teach each other, share Best Practices, exploit unique strengths of programs at other Hubs, share unusual expertise in an emerging methodology/technology, share high end instrumentation or scarce populations of people with unmet health needs. Examples include the proposed **"mini-sabbaticals"** and shared **"study section"** experience.
4) New and innovative programs to re-enforce the strengths of our scholars in a broad and deep spectrum of capabilities and to establish them as leaders in the field, not just for the pursuit of their own areas of interest, but as teachers of C/T Science to others. Examples are the recently established **novel PhD program in C/T Science** that was designed in response to feedback from and bidirectional communication with our scholars and designed to meet the needs of C/T researchers, our **"R01-bootcamp"** and the **"KL2-reunion."**
5) A robust education and career development program that utilizes all resources in the CTSA and synergizes with the TL1 pre-doctoral and postdoctoral programs. Examples include the **adaptive curriculum**, revamped multidisciplinary seminar series and, the **"K-Club."**

The KL2 Career Development Program has the following aims:

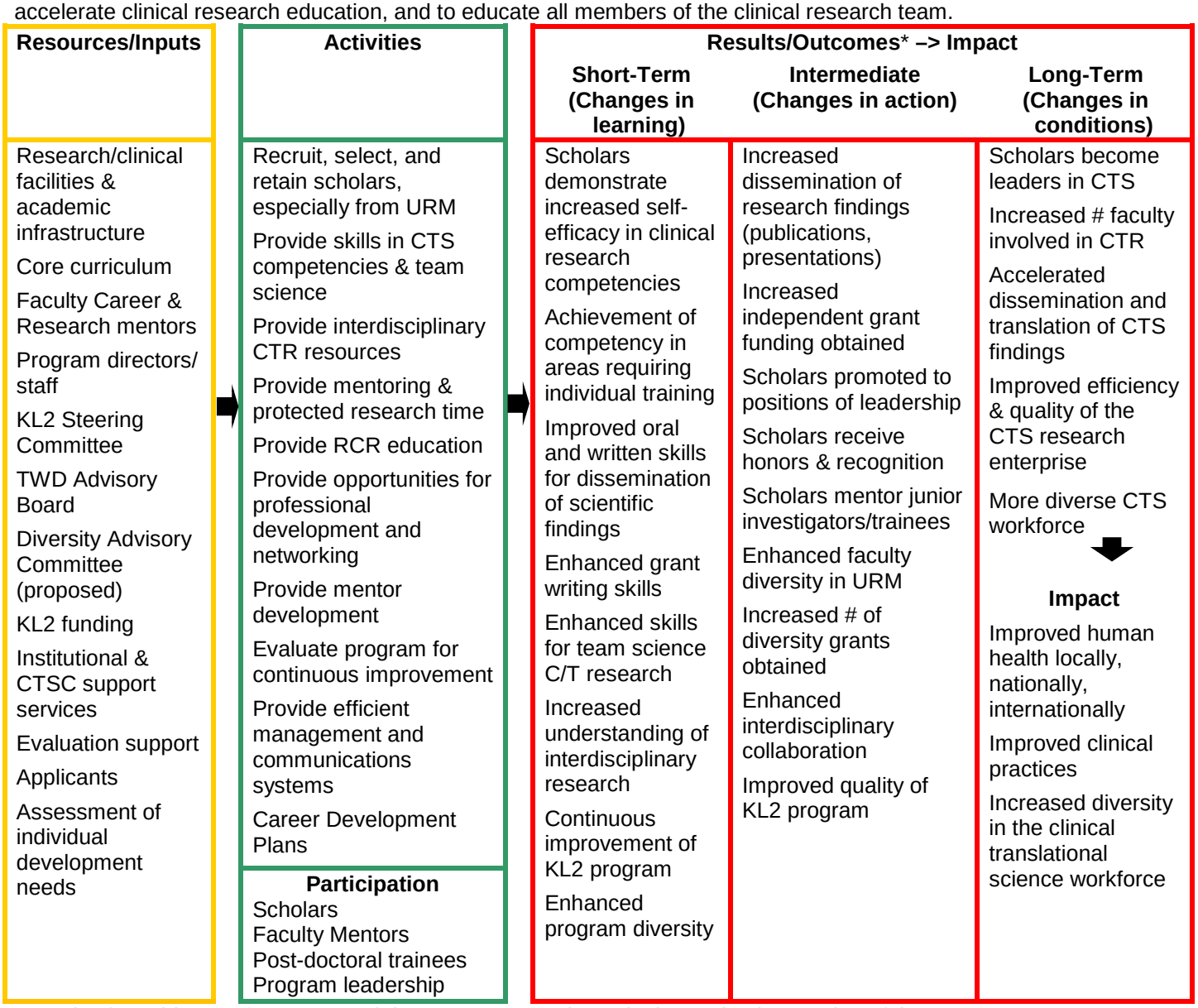
Aim 1: Further enrich and expand our integrated CTSC-wide innovative and individually tailored KL2 program designed for a select group of impactful and focused C/T scholars from diverse disciplines (including medicine, nursing, bioinformatics, social work, engineering, pharmacology, and psychology, etc.) who stand to gain the most from a multidisciplinary highly refined and personalized development program in team science and C/T research.
Aim 2: Prepare the next generation of investigators with the multidisciplinary skills required to lead cutting-edge C/T research and meet the opportunities and challenges of medicine in the 21st Century presented by a collision of biomedical disciplines, explosive expanding information-age collections of data, the rapidly expanding older population, and the expectation that the delivery of care will be increasingly personalized.
Aim 3: Build the multidisciplinary workforce of the future by collaborating with KL2 programs at other CTSA Hubs to share best practices, set the standards, and innovate in C/T career development

Our highly adaptive KL2 program focuses on addressing the individual gaps in knowledge and skill of each one of our scholars. Our current program benefits from our cross-institutional, cross-disciplinary clinical and translational research career development program, which, in turn, derived from the successful introduction of the Roadmap K12 multidisciplinary clinical/translational research program launched in 2004. At this point, we seek to improve the program by making sure that our select Multidisciplinary Clinical Research (CR) Scholars complete the program with the knowledge and skills to conduct outstanding cutting-edge multidisciplinary clinical research and to lead teams of investigators who recognize the importance of different research paradigms, ranging from molecular medicine to public health sciences, for rapidly translating scientific discoveries into better diagnostics and therapeutics. Specifically, our adaptive KL2 program will focus on:

1) Instilling appreciation for the theory, methods and analytic strategies of the diverse disciplines contributing to multidisciplinary clinical research through a rigorous and novel didactic program;
2) Developing clinical research leaders with strong team management skills, excellent verbal and written communication skills and outstanding grant writing skills; and,
3) Providing in-depth multidisciplinary mentored research experiences that serve to catalyze scholars' commitments to careers as multidisciplinary clinical researchers.

As we re-designed our program, we kept the best practices form our first two iterations, incorporated what we learned from our scholar feedback over the years, carefully considered the available institutional resources, the desired outcomes (what we do and who we reach), the results (short, intermediate and long term), the published literature[2-18] and the overall impact of the entire program. Figure 1 represents the logic model of our KL2 program. The specific areas including the metrics used for evaluation are presented in the relevant sections in the application.

Figure 1: CTSC Institutional Career Development Core ("KL2 Program") Logic Model: The goal of the KL2 Program is to educate leaders for the nation's multidisciplinary clinical and translational research workforce, to accelerate clinical research education, and to educate all members of the clinical research team.



* Metrics for evidence of success and data sources are shown in the evaluation section of the KL2 program.

PROGRAM PLAN:

Overview: Our KL2 program is grounded in and builds upon our successful existing KL2 program that began as a K12 program in 2004. We have learned to work seamlessly across CTSC-partner institutions and disciplines, and demonstrated that barriers to multidisciplinary collaborations can be surmounted by effective leadership and a common vision. The best practices we have learned (like having Career Mentors, regular career development reviews, multidisciplinary seminars, study section experience, etc.) will be implemented moving forward. Over the initial two cycles, bidirectional communication with our scholars resulted in significant improvements in the program. The education of the KL2 Scholars is adapted to the needs of individuals by a formal (anonymous surveys and one-on-one and group face-to-face meetings) and informal assessment by the CTSC Evaluator, Clara Pelfrey. Concepts gleaned from these evaluations are used in framing plans for educational interventions for other scholars, as well. This process will assure that we will continue to innovate as we support the development of the future leaders for the Nation's clinical research enterprise. A unique goal of our program is to transition scholars directly to independent (R level) funding following completion of the program. This is not a program that focuses on helping the candidate obtain additional mentored (K level) funding. Our scholars are

selected, in part, because of their motivation to follow a path toward independence after completion of the program and we have a strong track record in transitioning them to independent funding which allowed us to bend the curve of the rising age at the time of securing first R01. Between 2005 and 2015, we received 353 applications and provided awards to 63 scholars (including 4 scholars who participated in a one-time 2-year pilot program supported by their home institutions). Of the scholars who graduated from our KL2 program after four years of funding, 40% achieved R level funding at five years since the initial award (compared to a National average of 20%). At eight years 54% of our scholars achieved independent funding (compared to the National average of 40%). Over 80% of all our scholars are still in research and have received substantial, competitive funding from sources other than the NIH (major disease or philanthropic foundations like the American Heart Association or the Multiple Sclerosis Society, etc.). Our KL2 program has been able to achieve these rates of independent funding while lowering the average age of receiving first independent NIH funding in our scholar population to **39.93 years**, which is four to five years earlier than the current national average (Table A).

Table A. Independent grant funding obtained by KL2 alumni – Comparison to National average. National data from Yin et al,[19]

Category	Period	N	# with NIH funding	% with NIH funding	National average %	# with other funding	Total # Funded	Total % funded
TOTAL KL2 Applications	2005-2016	353	-	-	-	-	-	-
TOTAL KL2 Awarded	2005-2016	59	-	-	-	-	-	
5 years since KL2 award	2007-2010	20	8	**40%**	**20%**	7	15	75%
8 years since KL2 award	2005-2006	13	7	**54%**	**40%**	4	11	85%

Program Administration

Summary of program governance: The **Executive Committee** is composed of **Dr. Dweik (Director)** and three **Associate Directors (Drs. Harding, Spilsbury, and Moore).** This group will provide direct program management. These faculty and others will constitute a **Steering Committee** responsible for program governance. A TWD Advisory Board will provide broad oversight of the program. The Director reports to the CTSC PI (Michael Konstan, MD), the Dean of the School of Medicine (Pamela Davis, MD, PhD), and the TWD Advisory Board. An Administrative Director, Beth Spyke, will support program activities and grant management (in collaboration with TL1 and CTSC administrative leadership). Program leadership is drawn from all participating institutions. All program leaders and mentors have faculty appointments at CWRU SOM, SON or SOE. The institution of primary appointment/employment is indicated for individuals below (in some cases of balanced function and dual employment, two institutions are indicated).

Raed Dweik, MD is the Director of the KL2 program (CCF, CCLCM of CWRU). He is currently Professor of Medicine at The Cleveland Clinic Lerner College of Medicine of CWRU and Director of the Pulmonary Vascular Program in the Department of Pulmonary, Allergy, and Critical Care Medicine in the Respiratory Institute at the Cleveland Clinic. He is also a staff scientist in the Department of Pathobiology in the Lerner Research Institute. He maintains an active practice in Pulmonary and Critical Care Medicine with special interest in Pulmonary Hypertension (PH) and runs an independent research laboratory with continuous NIH funding since 2002. He has over 200 publications with an h-index of 44 (as of February 2016). The focus of his laboratory is on understanding the pathobiology of PH with a particular interest in pulmonary vascular biology, nitric oxide, and lung matrix. His research contributed to the findings of low nitric oxide (NO) in idiopathic pulmonary arterial hypertension (IPAH), and identified the hypoxic regulation of pulmonary NO. More recently, he described the dysregulation of hyaluronan (HA) production in PH. This novel discovery is the basis of a current 7-year NIH grant, which is part of the NHLBI Program of Excellence in Glycoscience (PEG) and an R01 (3rd percentile score, starting April 2016) exploring the mechanism of metabolic dysregulation in PH. As a former K23 recipient Dr. Dweik appreciates and strongly believes in the importance of mentoring and nurturing young researchers who are interested in translational research careers. As he leads this program, he draws on his own experience as a mentee and as a mentor. Over the past 12 years, he had the pleasure to be the mentor for several individuals at different stages in their training including 12 pre-doctoral and 37 post-doctoral trainees many of them went on to have very successful careers in medicine and research. His current and former trainees include KL2, K23, F32, and K99 award recipients. Dr. Dweik serves or has served on multiple NIH review panels. Between 2004 and 2009, Dr. Dweik served on the Mentored Patient Oriented Research Career Development

Awards (K18, K23, K24 and K25) study section and between 2005 and 2010 he served on the Mentored Clinical Scientist Development Award (K08) study section both of the NIH-NHLBI. He is currently a regular member of the NIH-NHLBI Respiratory Integrative Biology and Translational Research (RIBT) study section (2015–2019) and a member of the NCATS workforce development Domain Taskforce (DTF) which helps keep him aware and in tune with National trends and challenges as-well-as best practices in recruiting and developing the new generation of C/T scholars. The Director is also currently a member of and the recent past Chair of the Committee on Advancement, Promotion and Tenure (CAPT) at the School of Medicine, an experience that helps him provide insights to the scholars about the promotion process and how multidisciplinary research and team science is valued and evaluated.

KL2 Associate Director: Clifford V. Harding, MD, PhD (CWRU SOM/UHCMC) is the Joseph R. Kahn Professor and Chair of Pathology at CWRU and UHCMC. He has a long-standing productive NIH-funded research program on the regulation of immune responses during infection with *Mycobacterium tuberculosis* (Mtb) or HIV. He has over 190 publications (>10,000 citations, h-index = 55). His main current scientific focus is studying the mechanisms of immune evasion and persistence of infection in tuberculosis. He has been a leader in developing research training for PhD students, MD-PhD students and physician-scientists. He has been the Director of the MSTP at CWRU since 2001. He has served on the Steering Committee and multiple other committees for the AAMC GREAT MD-PhD Section. He has developed both basic and translational research training programs; he has designed and launched new training programs in Immunology and Cancer Biology (e.g. as founding Director of the Immunology Training Program at CWRU). He designed and launched the CTSTP that is the focus of this application and has directed the CTSTP since its launch in 2007. He worked with SON faculty to design the DNP-PhD program, and he contributed substantially to the design and launch of the new Clinical Translational Science PhD program (he continues to serve on its Advisory Board.). He has contributed to the national/international research community with service on numerous NIH and international study sections and through the American Association of Immunologists (e.g. as Chair of the AAI Committee on Public Affairs). Dr. Harding has mentored 27 PhD students and 11 postdoctoral fellows; those who have completed training have positions as medical school faculty (10 plus two pending faculty appointments), NIH scientists (two), and program leaders in industry (eight); others are still in training.

KL2 Associate Director: James Spilsbury, MPH, PhD (CWRU SOM) is Assistant Professor of Epidemiology & Biostatistics. He is Co-Director of the PhD program in Clinical Translational Science; Chair of the KL2 Curriculum Committee; and Director of the CTSC Academic Development Core, where he manages interdisciplinary educational and training activities. He directs Clinical Research Scholar's Program (an MS program) and a graduate certificate program in clinical research. He is a graduate of our KL2 program. Dr. Spilsbury is an anthropologist focused on the effects of social and cultural environment on children's health and well-being. His NIH-funded research investigates effects of neighborhood conditions on child maltreatment. Dr. Spilsbury is strongly committed to mentoring. He has served as the faculty advisor/mentor for numerous students in the MS program, and he has served as a dissertation committee member on doctoral students' committees in Clinical Translational Science, Anthropology and Social Work.

KL2 Associate Director: Shirley Moore, PhD, RN, FAAN (CWRU SON) is Professor and Associate Dean for Research in the SON. She is a behavioral scientist and PI of a P30 Center of Excellence in Self-Management Research. Her research addresses self-management of health and behavior change in child and adult populations, particularly health-promoting behaviors of dietary intake, physical activity & weight management. She is an expert in designing and testing interventions for behavior change. She has served as PI of several NIH-funded studies, and is experienced in building multidisciplinary teams of physicians, nurses, biomedical engineers, social workers, exercise physiologists, nutritionists, computer scientists, economists & statisticians. Dr. Moore has 5 past and 4 current predoctoral trainees and 5 past and 6 current postdoctoral trainees. Her trainees have attained NRSA, K01, KL2 and other grants; they include current faculty at 10 universities.

Dr. Dweik will be assisted by a **KL2 Executive Committee** to include all three Associate Directors:

- Raed Dweik, MD (KL2 Director, CCF, CCLCM)
- Clifford V. Harding, MD, PhD (KL2 Associate Director, CWRU SOM/UHCMC)
- James Spilsbury, PhD (KL2 Associate Director, Co-Director, C/T Science PhD Program, CWRU SOM)
- Shirley Moore, PhD, RN (KL2 Associate Director, CWRU SON)

The Executive Committee will manage the program to implement the decisions of the Steering Committee and Advisory Board and develop recruitment, curriculum, trainee advising and assessment of the program. Dr. Dweik will provide overall leadership. Dr. Harding will help maintain the seamless connection between the KL2 and the postdoctoral portion of the CTSTP, complementing his role as TL1 Director. Dr. Spilsbury will contribute to the KL2 curriculum and Clinical Translational Science PhD program. Dr. Moore will help oversee the DNP-PhD program and contribute to the KL2 core curriculum and professional development programs, particularly team science. All Executive Committee members also serve on the Steering Committee.

KL2 Steering Committee: The Steering Committee will make decisions regarding program policies; curriculum development; program guidelines; scholar selection/admissions; approval of mentors; tracking, evaluation and guidance of current scholars; and other issues facing the KL2 program. Steering Committee members will also individually provide scholar advising. The committee will track scholar performance, intervene to help when indicated, and make disciplinary decisions when needed, including dismissal from the program. **The KL2 Director will be Chair of the Steering Committee** which will meet at least monthly. He will also serve on all three subcommittees that will manage specific areas as indicated below and report to the full Steering Committee during the combined meetings. The full Steering Committee is the combination of the following subcommittees.

Recruitment and selection subcommittee:

- Raed Dweik, MD (Subcommittee Chair, KL2 Director, CTSTP Associate Director, CCF)
- Clifford V. Harding, MD, PhD (CTSTP Director, KL2 Associate Director CWRU SOM/UHCMC)
- Michael Rothberg, MD, PhD (Vice Chair for Research, Medicine Institute, CCF)
- Robert Bonomo, MD (Chief of Medicine VAMC)
- Wilson Tang, MD (CRU Director, CCF)
- John Kirwan, PhD (CCF)
- Fabio Cominelli (CWRU)
- Emina Huang (CCF)
- Michael Kattan (Chair of Quantitative Health Sciences, CCF)
- Geoff Vince (Chair of Biomedical Engineering (CCF)
- Randy Cebul (MetroHealth)
- Joseph Calabrese (CWRU)
- Patricia Higgins (CWRU)
- Stanly Hazen (Chair of Molecular and Cellular Medicine, CCF)

Mentoring and career plans subcommittee:

- Al Connors, MD (Subcommittee chair, Chief Medical Officer, MHMC)
- Raed Dweik, MD (Committee Chair, KL2 Director, CTSTP Associate Director, CCF)
- Neal Dawson, MD (Chair, KL2 Multidisciplinary Training Subcommittee, MHMC)
- Eugene Blackstone (CCF)
- Mukesh Jain, MD (Chief Scientific Officer, UHCMC)
- Patricia Higgins (CWRU)

Curriculum subcommittee:

- James Spilsbury, PhD (Subcommittee Chair, KL2 Associate Director, CTSTP Associate Director, Co-Director, C/T Science PhD Program, CWRU SOM)
- Raed Dweik, MD (Committee Chair, KL2 Director, CTSTP Associate Director, CCF)
- Clifford V. Harding, MD, PhD (CTSTP Director, KL2 Associate Director CWRU SOM/UHCMC)
- Shirley Moore, PhD, RN (KL2 Associate Director, CWRU SON)

Other at-large Steering Committee members:

- Paul MacDonald, PhD, Associate Dean for Graduate Education (CWRU)
- Clara Pelfrey, PhD, Evaluation Director, CTSC (CWRU)

Translational Workforce Development (TWD) Advisory Board: The TWD Advisory Board will meet 1-2 times per year and as needed to provide high-level oversight, advice on the balance of different objectives, review and outcomes assessment for the TL1, KL2 and other TWD aims of the CTSC. This will facilitate coordination and

synergies between the KL2 & TL1 programs, and the other CTSC programs with TWD goals.

- Mark Chance, PhD (TWD Advisory Board Chair, CTSC Associate PI, TWD Program Director, CWRU)
- Michael Konstan, MD (CTSC PI, CWRU)
- Robert Bonomo, MD (Chief of Medicine VAMC)
- Al Connors, MD (Chair KL2 Mentoring Committee, MHMC)
- Neal Dawson, MD (Chair, KL2 Multidisciplinary Training Committee, MHMC)
- Serpil Erzurum, MD (CTSC Associate PI, CCF)
- Stan Gerson, MD (Director, Case Comprehensive Cancer Center, CWRU)
- Jonathan Haines, PhD (Chair of Epidemiology and Biostatistics; Director of Informatics, CTSC; CWRU)
- Mukesh Jain, MD (Chief Scientific Officer, UHCMC)
- Robert Kirsch, PhD (Chair, Biomedical Engineering, CWRU)
- Li Li, MD (Director, Clinical Translational Science PhD Program, CWRU/UHCMC)
- Mary Kerr, PhD, RN (Dean, School of Nursing, CWRU)
- Jeremy Rich, MD (Chair of Stem Cell Biology and Regenerative Medicine, CCF)
- Anthony Wynshaw-Boris, MD, PhD (Chair of Genetics, CWRU)

This administrative structure will assure best practices in research education by coordinating research education across institutions and departments.

Institutional resources: Participating institutions include CWRU, CC, UHCMC, MHMC and VAMC. These sites have outstanding resources for cutting edge C/T research. CWRU SOM is a top tier research-intensive medical school, ranking 25th among some 140 U.S. medical schools in research (US News and World Reports, 2016 and 2017). CWRU and its affiliates garnered over $275M in NIH research funding in FY16. The SON is research-intensive, ranking 14th in the U.S. for NIH funding among schools of nursing (FY16) and 8th for DNP training (US News and World Reports, 2017). The SOE has over $40M in research expenditures. The Department of Biomedical Engineering, a joint department of the SOM and SOE, is ranked 15th by US News and World Reports (2017). Each year, CWRU SOM training programs include a total of approximately 100 MD-PhD students, 760 MD students, 430 PhD students, 590 MS students, 60 MPH students and 40 MA students. Clinical programs provide critical resources for training and research at CC (1268 beds), UHCMC (771 beds), MHMC (708 beds) and VAMC (586 beds). ACGME-accredited slots number 740 residents and 321 fellows at CC, 675 residents and 194 fellows at UHCMC, 308 residents and 56 fellows at MHMC. The VAMC has a total of 148 slots that are staffed by residents participating in residency or fellowship programs based at UHCMC, CC or MHMC. Numerous interdepartmental centers provide resources to promote research, training and collaboration among faculty members with different research backgrounds. Prominent examples include the NCI-designated Case Comprehensive Cancer Center, the Center for AIDS Research, AIDS Clinical Trial Unit, Geriatric Research Education and Clinical Center, Mellen Center for Multiple Sclerosis, Skin Diseases Research Center, Tuberculosis Research Unit, Center for Stem Cell and Regenerative Medicine, Center for Proteomics and Bioinformatics, Center for Global Health and Diseases and Visual Sciences Research Center.

Program Faculty

Mentorship is critical to the development of clinical investigators and to their progression through the stages of a successful research career. The KL2 program leadership will assure that one-on-one relationships between scholars and their research advisors are utilized to their full potential. This process is well under way in our existing KL2 Program. Responsibilities for Research mentors will be made explicit and include a minimum of the following: 1) Guide the new investigator in developing a feasible and appropriate proposal; 2) Assist in obtaining necessary resources and approvals; 3) Oversee performance of research projects, providing guidance in presenting research to colleagues and outside observers; 4) Provide an appropriate level of interaction, through regular individual meetings, attendance at research group meetings; 5) Teach content-specific knowledge where appropriate; 6) Provide encouragement and promote self-confidence through organized successes, sharing of information, and constructive feedback and criticism; 7) Take special interest in professional development of the new investigators; and 8) Teach and demonstrate the importance of collaboration, teamwork, and networking; 9) Provide support and guidance in Grant submissions and publications.

Each Scholar is guided by two mentors, a Research Mentor and a Career Mentor (Table B). The **Research Mentor** is responsible for research supervision and research career development. He or she is expected to meet with the clinical research scholar on a weekly basis throughout the duration of the program. The Research mentor must be an active, independent clinical investigator and have a successful track record of mentoring clinical investigators. The **career mentor** must be from a different clinical research discipline than the research mentor. The career mentor supports the scholar's academic planning, assists in understanding and managing participation in the overall program, provides a multidisciplinary perspective on the scholar's career development plan, and helps the scholar develop multidisciplinary research. Both the career and research mentors participate in local and national evaluation activities. One of the lessons we learned from our experience is the importance of bidirectional communication and learning. Not only do the mentees benefit from this interaction, but the mentors learn from the KL2 scholars as well. The close relationship the scholars develop with their mentors over the four years of the program helps the scholars navigate the frustrating path of seeking career positions and helps them understand the importance that they develop passion about their work that will enable them to persist. On the other hand, our frequent evaluations and feedback from the scholars also allow us to provide flexibility in mentor relationships so that the KL2 scholar can have multiple research mentors, either simultaneously or sequentially, if circumstances require it.

Table B: Research and Career Mentor responsibilities

Responsibilities	Research	Career
Yearly orientation	✓	✓
Scholar meetings	Weekly	Every 2 months
Joint Career Development	✓	✓
Planned Program of Study	✓	✓✓
Career Development Plan	✓	✓
Development of Research Proposal	✓✓	✓
Review of Research Proposal	✓	✓
Assure integration and balance between didactic, research and clinical components	✓	✓✓
Twice yearly progress reports	✓	✓
Evaluation activities	✓	✓

We are very fortunate because we are able to draw on a large pool of faculty from all partnering institutions. This allows us to be selective in building our mentoring pool to take into account complementary expertise and experience, previous mentorships, active research, and scholarly activities. All mentors are proposed by the program director and reviewed by the mentoring sub-committee of the steering committee before final selection. Mentors who have not performed well or who have been perceived by their mentees as unfavorable are removed from the mentoring pool. While we take requests to change mentors very seriously, our guiding principle is the welfare of the scholars. Fortunately, over the past 10 years, we changed mentors only twice. Table 2 provides a sample of mentors available to the Scholars and their research interests.

Responsibilities of the research and career mentors are outlined in the accompanying table.
Mentees also have responsibilities to:

- Seek and incorporate career, professional and personal advice on issues of teaching, research, promotion, tenure, and the collegial culture
- Stay in touch with regular communication with team members
- Live up to commitments and be on time and timely with work responsibilities
- Be available for networking opportunities and introductions to key individuals by mentor
- Plan together as a team and practice shared decision-making based on shared expectations
- Listen…Be honest…State goals clearly…Take the initiative…

Participating faculty include 65 approved primary scientific mentors **(Table 2),** including 52 in the School of Medicine, two in the School of Nursing, and 11 in the School of Engineering. Potential mentors are all CWRU faculty some of whom are located at each of the affiliated hospitals; they are included in these numbers based on their School in which they hold their primary CWRU faculty appointment. There are additional program faculty (not included in Table 2) who will not serve as primary scientific mentors but will serve as co-advisors or career

mentors, or contribute to program activities. The participating faculty represents strengths in all appropriate areas of C/T research and include physicians, nurses, dentists, PhD researchers with C/T research interests, biomedical engineers, informatics, social scientists and others. They are all productive C/T researchers with externally-funded research programs. Current and prior KL2 scholars have been mentored by over 70 of our faculty. Overall, the participating faculty will support rigorous transdisciplinary research as well as in-depth mentoring in specific areas of research.

Mentor approval and assessment: KL2 mentors must be approved by the KL2 Steering Committee. The program will actively develop the mentor pool as new candidates become available. Prospective mentors submit their CV, funding data and training record. In the case of junior faculty with a limited track record, a letter of recommendation from the department chair is required. The Steering Committee reviews and votes on each application to determine whether to grant approval either as a Senior Mentor (well established research program, NIH funding and training record) or an Initial Mentor (e.g. a promising junior faculty member with a more limited training record who is on a strong research trajectory—see Mentor Development, below). Existing mentors will be reviewed annually to confirm that the criteria for approval are still met. If a mentor does not provide appropriate mentoring, mentor approval will be removed. Assessment will include mentee feedback gathered in a regular ongoing manner.

Criteria for mentor approval include: 1) Strong scientific productivity and leadership of a well-developed independent research program that will allow trainees appropriate access to and "ownership" of cutting-edge research projects. 2) Consistent record of extramural funding as P.I. (NIH R01 grants or equivalent; this may be adjusted for promising new junior faculty with a strong letter of support from their Chair). 3) A track record of successful prior mentorship (may be waived for Initial Mentors, but they must have a Senior Mentor as a Co-Mentor, a strong letter of support from their Chair, and a plan for mentor development).

Mentor development: We will require that all Initial Mentors participate in a Mentor Development Program, and we will strongly encourage Senior Mentors to participate in this program. Mentors will receive training through resources at ctsacentral.org (https://ctsacentral.org/consortium/education-and-training/, e.g. the Mentor Development Programs Course Materials from UCSF). The TL1 and KL2 will develop mentor training forums, including discussion of literature on mentoring (see https://ictr.wisc.edu/MentoringPublicationsReports). An Initial Mentor must have an approved Senior Co-Mentor for any trainee; the senior co-mentor may or may not be a collaborator but he/she must participate actively in advising and oversight of student progress. The Initial Mentors will be guided and mentored in developing their own mentoring skills by the Senior mentor. These arrangements allow talented junior faculty to participate in the mentor pool and develop their mentoring skills.

Cross-institutional participation and interactions: KL2 participating faculty are located in the SOM, SOE, SON and all CTSC affiliates (CCF, UHCMC, MHMC, VAMC). The SOM is adjacent to the rest of the CWRU campus, facilitating collaborations with the SOE, SON and other schools. CCF, UHCMC and VAMC are all within walking distance of the SOM, and MHMC is only 25 minutes away by car. KL2 scholars have been mentored at laboratories at CWRU, UH, CCF, VAMC and MHMC. The new PhD program in Clinical Translational Science has engaged mentors at all affiliated sites, and the three initial trainees in this program are at CCF (one), MHMC (one) and UHCMC (one). Many KL2 scholars have mentors, co-advisors and/or collaborators at multiple sites.

Mentoring record: The mentors have established mentoring records, with many prior mentees having successfully established independent research programs. Table 8C shows current and past postdoctoral scholars, Table 2 shows the participating faculty. In addition to established senior faculty mentors, we encourage junior faculty to develop mentorship skills; this is facilitated by a mentor-development program that is run through the KL2 program and a requirement for junior mentors to have a senior mentor as co-advisor for scholars (junior mentors defined as those who have not established a substantial record as a mentor, e.g. having productively mentored postdoctoral scholar to successful independent later stages of a research career).

Proposed Career Development Program

We regard **Program Flexibility and Adaptability** as an essential source of the strength of our career development plan in meeting the needs of our KL2 scholars in order to provide unique, customized, career development for every scholar. The KL2 scholars and their mentors meet with the KL2 leadership individually when they enter the program. They reach a consensus about the scholar's established strengths and competencies and together they formulate the career development plan to meet the scholar's needs. Scholars

who enter the program with demonstrated proficiency in any of the domains comprising the core curriculum may, in consultation with the KL2 leadership and mentors, substitute other specialized coursework for core courses, take courses to complement their existing skill set, or participate in a wide range of local and national educational and skill-building activities: e.g., summer short courses, workshops, clinical observerships for non-clinicians, described in a published article jointly co-authored by our KL2 scholars[1], mentoring meetings with non-local experts. Within six months of starting the program, KL2 scholars must construct a career development plan (**Table C** is an example of an actual plan), which is reviewed by the Mentoring sub-Committee. Career plans include career goals for the next five years. For each goal, scholars specify two to five objectives that, when met, will result in achieving that career goal. For each career objective, scholars specifically list educational and research activities necessary to meet the objective. For each objective, they are also asked to indicate what individual products (courses, degrees, publications, presentations, or grants) are expected. Finally, scholars are asked to put together a two-year timeline, displaying individual objectives, educational activities, research activities, and products. This challenging exercise has become an important tool, allowing scholars to benchmark their own progress, and program leadership to track scholar progress. Further, they provide an excellent vehicle to foster career-related discussions between scholars and their mentors. They encourage Scholars to articulate their goals and to choose wisely those educational and research experiences that directly apply to their goals. Table C shows an example of an abbreviated CDP and review/evaluation criteria.

Table C: Example Career Development Plan				**Example Review/Evaluation Criteria**
Vision Statement (Abbreviated): It is my intent to further develop my professional and research career with a focus on multiple sclerosis (MS). I will concentrate on the study of progressive forms of MS with an emphasis placed on advanced imaging methods, novel clinical outcome methods, and the application of innovative clinical trial design. Expertise will be achieved through course work, mentored research, and professional exchange in a transdisciplinary framework. It is my ultimate goal to be able to lead and direct a team of investigators to produce research that has the ability to directly impact the care of patients with progressive MS. I am also pursuing a PhD in clinical investigation which will combine required courses of the KL2 award curriculum with trans-disciplinary classes, which have a more specific impact on my research area. My thesis will focus on the use of MRF in MS.				• **Research topic significant?** • **Innovative study approaches?** • **Combination of KL2-supported activities positions Scholar to conduct multidisciplinary, team-science research?** • **Marketable Scholar in terms of career placement?**
Grant Submission Timeline: a.NMSS Pilot Grant Vitamin D/SPRINT MS study, Oct 2015 b.NIH R01 submission: Longitudinal Study of Magnetic Resonance Fingerprinting, Mar 2016. c.NIH/NMSS Clinical trial submission of potential remyelinating agent (Ketoconazole), Feb 2016				• **Trajectory of proposed studies logical and scientifically sound?** • **Appropriate funding sources?** • **Timeline feasible?**
Goal 1: **Develop expertise and recognition in advanced magnetic resonance imaging (MRI) modalities**				• **Contribution to Career Vision?** • **Reasonable goal in KL2 timeframe?**
Objectives	**Educational Activity**	**Research Activity**	**Product/Dates**	
1. Develop expertise in measurement of cortical thickness.	• Training in Dr. Elizabeth Fisher lab cortical atrophy measurement.	• Cortical thickness analysis of mesenchymal stem cell (MSC) trial (Completed 22/24)	• Abstract Cortical thickness ECTRIMS 2015 • Manuscript of vitamin D levels in relation to disease metrics in MSC trial (pending analysis) Abstract May 2015	• **Objectives scientifically sound and feasible?** • **Objectives collectively reflect multidisciplinarity and team science?** • **Completion of educational & research activities will produce desired objective?** • **Adequate expertise identified?** • **Workable balance of coursework and research activities?** • **Coursework appropriate in content and timing** • **Products concretely defined?** • **Benchmarks in place?** • **Product timeline feasible?**
2. Develop expertise in diffusion tensor imaging		• Complete validation of tractography versus region of interest (ROI) diffusion tensor imaging (DTI) methodology. (Completed) • DTI analysis of lesional tissue from MSC trial. (Completed 24/24) • DTI analysis of normal appearing white matter from MS dataset	• Abstract ECTRIMS 2013 • Abstract Submitted and accepted AAN 2014 • Manuscript of advanced imaging methods in MSC trial	
3. Establish sound scientific basis of MRI physics and database management	• Course work in MRI physics (EPBI 410)	• Establish observational study of MRF in MS • Establish sequences • Detailed data management plan	• Attend and present research at an MRI methodology conference (ISMRN)	
4. Development of MRF in MS	• Informal coursework with Vikas Gulani Apr-Aug 2015	• Protocol for pilot study of MRF in thalamus, funds secured • 20 subjects. Start Apr 2015	• Manuscript preliminary data from MS subject P50 cohort Oct 2015 • Manuscript Pilot Study Jan 2016 • R01 Application Mar 2016	
Goal 2: **Development expertise in clinical trial design**				**(see above)**
1. Develop core academic knowledge for clinical trial design and trans disciplinary research.	• CRSP 501 & 502 • KL2 seminars • EBPI 490 completed • EBPI 465 completed • EPBI 437 completed • EBPI 438 completed • EBPI (701) thesis • EPBI 445 ethics	• Proposal for pilot funding Vitamin D levels in Progressive MS. • Proposal of remyelinating agent in MS (ketoconazole) phase II clinical trial	• NMSS grant submission Oct 2015 • NMSS/NIH Grant for Phase II study of ketoconazole in MS study Oct 2015 • Coursework completed	

Mentored Research Experience

The mentored clinical research practicum, a cornerstone of the scholar's program, is rooted in the conviction that clinical research is a complex process that is ideally performed by a group of experts from different disciplines using an integrated team approach. Mentors model and seek to transmit to their mentees a set of attitudes, skills, and behaviors required for developing multidisciplinary team-based clinical and translational research projects. There are two types of research experiences for scholars.

- (Optional) The scholar has the option to be an active team member, working alongside the mentor and his/her team. This type of experience will typically begin in the first year, but could extend through the second year. While the CR scholar is not expected to develop a formal research proposal for this experience, it is expected that the experience will result in concrete products such as presentations at national meetings, abstracts and/or publications.

- (Required) The scholar develops and implements at least one new clinical research project under the guidance of the research mentor. This is the central research experience for the scholar. The project addresses research questions central to the career path of the individual scholar and is expected to incorporate multidisciplinary team-based research experiences. The scholar writes a clinical research proposal that is reviewed and approved by the mentors and the mentorship sub-committee. The project usually receives ongoing support by the Scholar Resource Facility and is under the direct supervision of the research mentor. These more traditional types of research projects typically begin in the first year of participation and extend up to the fourth year, depending on the scholar. The mentor is responsible for suggesting needed modifications to the proposal to optimize inclusion of multidisciplinary collaborations and team-based research environments.

Figure 2: Proposed KL2 Core Curriculum
numbers in parenthesis represent credit hours

Summer Year 1	Year 1 Fall	Year 1 Spring
CRSP 401: Introduction to Clinical Research (3)	-----RESEARCH-----	-----RESEARCH-----
	CRSP 402: Epidemiology/Study Design (3) CRSP 412: Communication in Clinical Research-Grant Writing (1) CRSP 431: Statistical Methods (3) CRSP 501: Team Science-Working in Interdisciplinary Research Teams (1) *Scholar Seminar (0)*	CRSP 413: Communication in Clinical Research II – Presentations & the Mass Media (1) *Scholar Seminar (0)*
Summer Year 2	Year 2 Fall	Year 2 Spring
-----RESEARCH-----	-----RESEARCH-----	-----RESEARCH-----
	CRSP (new) Clinical Informatics (1) CRSP 603 Research Ethics & Regulations (2) *Scholar Seminar (0)*	CRSP 502: Leadership Skills for Clinical Research Teams (1) CRSP 503: Innovation and Entrepreneurship (1) *Scholar Seminar (0)*

Multidisciplinary Clinical/Translational (C/T) Research Curriculum (Figure 2)

Through appropriate formal coursework, other educational opportunities (workshops, observerships), and individualized mentoring, KL2 scholars will receive specific education to achieve a high level of expertise in their specific field. In addition, scholars will take a proposed KL2 core curriculum that aligns with nationally developed competencies for C/T research[20] and provides scholars with both the basic methodological skills to conduct C/T research and the core professional skills needed to become a successful interdisciplinary C/T researcher.

Concerning research methods skill development, all scholars take or demonstrate proficiency in three basic study design and biostatistics courses: CRSP 401 Introduction to Clinical Research, CRSP 402 Epidemiology and Study Design, and CRSP 431 Statistical Methods. Other required courses are specifically designed for the KL2 program to enhance professional skills: CRSP 412 Communication in Clinical Research—Grant Writing (strategies to increase writing productivity, development of compelling grant proposals, the grant review process); CRSP 603 Research Ethics and Regulation (IRB and HIPAA challenges, research with vulnerable subjects, research in the developing world, research in infections, stem cells and genetics); CRSP 501 Team Science—Working on Interdisciplinary Research Teams (understanding and using differing disciplinary mental models, conflict management, trust-building, group decision-making skills); CRSP 502 Leadership of Clinical Research Teams (developing effective leadership style and skills, assessing team members' learning styles,

optimizing management techniques); CRSP 503 Innovation and Entrepreneurship (translating academic research into commercial use, goals and objectives of businesses, technology development and transfer); CRSP 413 Communication in Clinical Research—Scientific Presentations and Working with the Mass Media (techniques making high-quality oral and poster presentations, strategies for working effectively with the mass media to disseminate research to the public) and CRSP Clinical Informatics (a new course providing core concepts and technologies related to the use of data from electronic medical records). See appendices for syllabi of multidisciplinary C/T research curriculum.

Each year of the program, all scholars participate in a year-long seminar. This series was developed by and for the scholars and meets bi-weekly for three hours. The Seminar Series covers special topics in C/T research (e.g., complex, adaptive systems, balancing strategies including propensity scores, qualitative methods, heterogeneous treatment effects) and skills for success (e.g., biomedical writing, grant preparation, presentation skills). The faculty facilitator, Dr. Neal Dawson, guides the discussion to achieve interdisciplinary dialogue and to challenge the scholars to think beyond their disciplinary silos.

Table D: Tracks / Options Available to Post-Doctoral Scholars

Course	PreKL2 PostDoc	KL2 (17 hrs)	CERTIFICATE (11 hrs)	MS (36 hrs)	PhD (54 hrs)
Innovation & Entrepreneurship	Elective	**Req**		Elective	Elective
Team Science –Working in Interdisciplinary Teams	Elective	**Req**		Elective	Elective
Leadership of Clinical Research Teams	Elective	**Req**		Elective	Core Elective
Communication In Clinical Research - Oral Presentation, Posters, Mass Media	Elective	**Req**		Req	Req
Communication in Clinical Research - Grant Writing	Elective	**Req**		Req	Req
Research Ethics & Regulations	Elective	**Req**	Req	Req	Req
Introduction to Clinical Research		**Req**	Req	Req	Req
Epidemiology/Study Design		**Req**	Req	Req	Core Elective
Statistical Methods I		**Req**	Req	Req	Req
Clinical Informatics		**Req**			Core Elective
Translational & Patient-Oriented Theory					Req
Meta-analysis & Evidence Synthesis					Req
Clinical Translational Science Seminar					Req
Additional Electives				10 cr	11cr
Other requirements				MS Thesis 9cr	PhD Thesis 18cr 2 Pubs

Synergy with Existing Programs: Courses that comprise the KL2 curriculum are also used jointly by multiple programs, thereby catalyzing interaction among KL2 Scholars and individuals from a wide range of disciplines and backgrounds who are in postdoctoral programs, residency programs, as well as matriculants in C/T certificate and degree programs (Table D). Professional skills courses are electives for the TL1 Post-Doctoral Program. By completing the core curriculum, KL2 scholars fulfill requirements for CWRU's Graduate Certificate in Clinical Research, and substantial portions of the coursework required for the MS in Clinical Research and the newly launched PhD in Clinical Translational Science. Depending on their individual knowledge gaps, development needs, and career trajectory, KL2 scholars may obtain one of these degrees.

Institutional training grants: The KL2 program will provide postdoctoral C/T research development to meet the TWD goals of the CTSC. This section describes other training grant resources at CWRU SOM and indicates the unique aspects of the KL2 in supporting C/T research training. Research training at CWRU is supported by our CTSA (including KL2 and TL1), our NCI-designated Case Comprehensive Cancer Center (with a K12 program) and NIH training grants, of which 26 include CTSTP mentors. These programs provide a rich set of resources and community for research training, yet the KL2 program is unique among them in supporting the breadth and type of C/T research training proposed in this application. The TL1 and KL2 are the only training grants to develop key areas of C/T training, such as team science and transdisciplinary research. No other training grant supports the PhD program in Clinical Translational Science. No other training grant encompasses the breadth of C/T research within its mission; other grants are focused on specific scientific or disease fields. The KL2 will uniquely develop the C/T goals for the participating scholars.

Collaboration with TL1: We aim to optimize both programs by fueling enthusiasm for careers in C/T research and by encouraging a dialog across a broad range of individuals. The idea is to open all the participants in both programs to the notion of cultural exchange and multidisciplinary science in a non-threatening environment which fosters interdisciplinary, team-based C/T research. The TL1 and KL2 will share a mentor pool, advisory board, team science curriculum, research training components, and professional development activities. Our new goals coupled with our prior innovations in the TL1 and KL2 programs will create a full pipeline of training across predoctoral, postdoctoral and KL2 scholar stages to train successful independent C/T research leaders. The KL2 program will also continue to share an annual retreat with the CTSTP/TL1 program.

Innovative educational solutions to personalized education and development:
As part of the KL2 Program's new initiative to expand the opportunities for Scholars to network with each other and to provide valuable career development content, we have conducted a focus group and key informant interviews with individual K program and awardees in the Cleveland area. Our goal is to use the information obtained from these interviews to inform the content of the K-Club with regard to the areas and subjects that are of most interest to mentored career development positions outside the KL2 program. Combined with several years of data from exit interviews with KL2 Scholars, this information provides valuable data with which to design a relevant K-Club professional development series that would have broad appeal to all K scholars and post-doctoral TL1 trainees who are approaching eligibility to apply for K awards. The interviews highlighted broad themes that all mentored career development scholars want and need to be successful.

Innovative concepts in our proposed program include:

- Infusing a culture that values multidisciplinary, team-based research by developing needed support and necessary skills for team-building and leadership education that emphasizes working across institutions and disciplinary silos;
- Capitalizing on our existing combined degree programs in clinical investigation. While scholars enter the program with an advanced degree, some may benefit from further formal education leading to a degree in another related discipline.
- Implementing learner-centered instructional methods such as problem-based learning seminars, mini-retreats, and the use of alternative approaches to education that adapt to individual learning styles and scheduling, access, and special issues that use all available communication tools including modern electronic media (DVDs, Internet-based curricular initiatives, webcasts) to facilitate accelerated, life-long learning.
- Enhance our current plan to further increase the number of underrepresented minorities and women in our KL2 program.

Specific programmatic innovations recently implemented or planned moving forward include:

KL2 Reunion: This event was started in response to scholar feedback over the years requesting informal functions to interact with current and former scholars. An inaugural KL2 Scholar and Alumni reunion was held in February 2015 and has been held annual thereafter. This gathering is intended for current, former and incoming scholars. After a welcome by Dr. Konstan and Dr. Dweik the current scholars present their work in short "elevator" speeches and invite attendees to learn more about their research by visiting their posters. Oral presentations and posters are judged by KL2 alumni, and a top prize is awarded in each category. The **KL2 Reunion** is intended to provide a forum for interaction and collaboration between current and former scholars and mentors in a social environment that fosters informal interaction.

K-Club: We believe the learning experience at the scholar level works best with a critical mass of participants of about 10–20, who grow into the culture of learning and challenging each other and collaborating from the perspective of different disciplines. The K-Club is designed to provide a regular, institutionalized forum for the exchange to occur and will help compensate for the reduced number of scholars (from 16 to nine). The earlier, larger program provided us the opportunity to develop and refine an innovative program. We will capitalize on the lessons learned to maintain our best practices with the smaller cohort, as we turn our attention to leveraging the KL2 scholars to advance C/T training more broadly across our institutions and nationally. We established a **K-Club** to sustain the cohesiveness of the scholars' experience at the CTSC institutions and to provide a sense of participation in a diverse, multidisciplinary, scientific environment. The **K-Club** will provide different levels of involvement / membership:

- For individuals seeking to apply for a K or already enrolled in a post-doctoral TL1 program (pre-K), we will invite them to attend open forums of the KL2 program like the outside speaker series.
- For individuals who have already received individual K awards (K23, K08, K99, etc.), we will invite them to attend the speaker series. A select group (up to 6) who are involved in interdisciplinary research similar to our KL2 scholars will also be invited to participate in the KL2 scholar seminar series.
- For individual who have recently successfully transitioned from a mentored (K, award) to independence (post-K), we will invite them to our annual reunion event and as guest speakers in the KL2 seminar series.

The **K-Club** will:

- Enhance the utilization of our resources (education, mentoring, etc.) without incurring any additional costs
- Allow us to expand the cohort size to the critical cohort mass needed for education in multidisciplinary research and collaborations
- Develop the next generation of mentors by allowing the KL2 scholars to mentor pre-K candidates and Post-K scholars to mentor pre-K and K scholars.

Grant-writing "Boot camp": This is another innovation that was designed based on bidirectional communication with scholars who helped design and critique the program as well as each other's applications. It will provide guidance with R01 and other grant applications beyond what is provided by the primary research mentor and the didactic courses. This is a **Grant-writing Basic Training Program** designed for Third and Fourth year scholars that includes all the steps required for grant applications and approval including a mock study section. This will make sure the scholars are on track and have the appropriate skills and access to the necessary resources for a successful independent funding. The program includes:

- A specific requirement in the CDP to provide a timeline for independent grant applications
- A dedicated meeting with the program director (Dr. Dweik) at the beginning of year 3 to specifically go over plans already developed with the research and Career Mentors for independent funding
- A focused, specific AIMS presentation in the seminar series to be critiqued by other scholars and mentors
- Pairing with a senior well-funded investigator (other than the mentors) to read and critique the grant application(s)
- Sitting on our own KL2 scholar study section/selection committee to experience and understand how study sections work

The experience of sitting on a study section was hugely popular with our senior scholars and stemmed from the Director's own experience. The first time he served on a study section, Dr. Dweik immediately recognized how helpful it would have been to have this experience before (not after as it is traditionally the case) submitting his first grant. Many of our scholars had the same exact feeling when they participated in our KL2 study section which has encouraged us to continue this practice moving forward. This program is being rigorously evaluated, and, if it meets our standards for acceptable quality, we will **suggest dissemination to other CTSA Hubs. We will explore this program expansion as a potential way to interact with other CTSA Hubs by having scholars from one site serve on another site's KL2 study section and vice versa.**

Scholar Cohort-Based Multidisciplinary Teams: This evolved out of our Multidisciplinary seminar series and involves establishing Multidisciplinary Teams of Scholars across cohorts (different years of entering the program). Senior scholars lead these teams with the goal of providing experiential learning and project enhancement. Every team member works to understand the perspective of the team leader (a fourth year scholar) regarding his/her research project and will contribute to it by discussing ways that perspectives gleaned from each team member's disciplinary area may advance the depth and especially the breadth of the project. Creativity is needed in this respect. For the team meetings, a time keeper and recorder will be designated and records of the meeting made available to and kept by the team leader. Lessons learned by the team leader and members are incorporated into the yearly project presentation in the KL2 Seminar. This report includes the interactions with other contributors to the research project such as content experts who are outside of the scholar's discipline.

Mini Sabbaticals: In order to provide personalized education and development opportunities for our scholars, we propose this novel concept of mini sabbaticals taken outside the CTSA Hub institutions and outside the reach of the established mentors. With appropriate justification and approval, KL2 scholars are permitted to pursue educational opportunities outside CTSC for a term not to exceed six weeks. The idea evolved out of the program director's (Dr. Dweik) successful use of the "**post-doc-in-a month"** approach in the training of his postdoctoral

fellows. This involves going on one (or more) trip(s) and spend time at another institution in order to develop a new skill or establish a new collaboration. Several of our scholars recently took advantage of these **mini sabbaticals** and spent time in another institution of their choice to learn a new skill or technique that is important to their research but is not offered at our five participating institutions. A fourth year scholar spent time at another institution to develop skills in using 7T MRI imaging for clinical Research in Multiple Sclerosis. He ended up collaborating shared research projects involving sequence details and post processing methodology. One of our first year scholars visited another academic center to learn more about agent-based modeling & incubator for Health Researchers which allowed him to receive hands-on training with AnyLogic software from one of the leading experts in agent-based modeling. This also provided our scholar the opportunity to interact with other experts and colleagues in the field. A third year scholar traveled to learn more about Functional Magnetic Resonance Imaging of the Brain. She spent a week learning the newest MRI image processing techniques and modifying them to analyze the data she is acquiring on patients with amyotrophic lateral sclerosis (ALS). The opportunity also allowed her to meet with other researchers who are using MRI to study ALS patients. **In the future, we propose to use these mini sabbatical opportunities to foster collaboration with other KL2-CTSA Hubs where our scholars would preferentially go to other CTSA Hubs for learning experiences and KL2 scholars from other CTSA Hubs would be encouraged to come to our site to learn.**

Clinical Translational Science PhD program: This recently established PhD program in clinical translational science evolved out of the identified needs of our KL2 and TL1 programs and is designed to meet the needs of C/T researchers. While all KL2 scholars already have a graduate degree, depending on their individual knowledge gaps, development needs, and career trajectory, some KL2 scholars may choose to obtain an additional degree. This novel PhD program was launched in 2015 and accommodates our two training pathways: "Postdoctoral" PhD training (KL2) and predoctoral combined degree MD-PhD training (TL1). The program provides trainees with professional and research skills to become productive researchers in C/T science. The curriculum totals 69 credit hours and is based on nationally-developed core competencies for this field. The 18 credit hour required core curriculum covers four key domains: 1) clinical and translational theory, practice, and perspectives ("Translational and Patient-Oriented Theory," "Seminar in Multidisciplinary Clinical & Translational Research"); 2) research methods ("Meta-analysis and Evidence Synthesis," "Study Design and Epidemiologic Methods"; 3) statistical science (core topics including linear and logistic regression, survival analysis, power analyses, modeling); 4) professional development ("Team Science-Working in Interdisciplinary Research Teams," "Leadership Skills for Clinical Research Teams," "Grant Writing," "Oral Presentations, Posters, and the Mass Media"). Elective coursework is selected based on individuals' field-specific knowledge-base & statistical/methodological needs: e.g., immunology, neurology, cancer, structural equation modeling, qualitative/mixed method approaches, clinical informatics, data management, clinical trial design, and comparative & cost effectiveness analysis. Trainees are fully immersed in research activities through research rotations and then PhD dissertation research. The program's interdisciplinary 42 core faculty members involve all CTSC institutions and numerous departments and centers, including the Case Comprehensive Cancer Center; the Centers for Clinical Investigation, Proteomics & Computational Science; the Departments of Epidemiology & Biostatistics, Pharmacology, Genetics, Family Medicine and Community Health, Molecular Biology and Micro-Biology; the Frances Payne Bolton School of Nursing; the School of Dental Medicine; the School of Engineering; and clinical departments at all CTSC affiliates. Program faculty are involved in a wide range of clinical and translational research domains: e.g. genetic/molecular epidemiology of cancer, cystic fibrosis, kidney disease, diabetes, and other complex diseases; pharmacogenetics; infectious diseases and antimicrobial resistance; innate immunity; medical decision making; cardiac rehabilitation; behavioral interventions; medical anthropology; oral health in special-needs populations; health disparities.

Program Evaluation:

CTSC Program Evaluation integrates data tracking and evaluation for multiple CTSC resource cores, incorporating a utilization-focused, participatory, and methodologically flexible approach. Our strategy is based on the CDC Framework for Program Evaluation and on the American Evaluation Association Program Evaluation Standards[20]. We are actively involved in collecting and using the NCATS Common Metrics for strategic planning, allowing us to align our evaluation efforts with the NCATS Consortium. We apply evaluation processes and findings to priority-setting, program accountability, and continuous quality improvement, distributing evaluation effort across the institute. Our evaluation domains, metrics and how data are used are summarized below and conform to our logic model. Additional key elements of CTSC Program Evaluation include the Evaluation Workgroups, the External Advisory Board (EAB), and the Request Management System (RMS) for tracking and evaluation efforts across all cores.

Approaches and Values: Drs. Pelfrey and Higgins designed our program's evaluation plan using the guiding principles established by the American Evaluation Association[21]. The principles include systematic inquiry, competence, integrity/honesty, respect for people, and responsibility for general and public welfare. These principles will continue to guide program evaluation and tracking decisions. We will continue our efforts to publish findings and contribute to the growing understanding of the educational programs, mentoring expectations, and research support necessary for successful preparation and career development of scholars in C/T sciences and multidisciplinary research collaborations. We published our career development plan (CDP) approach[22] and continue the use of career development plans as a tool for successful development of scholars in CTS and multidisciplinary collaborations. Program Evaluation of our KL2 Career Development Program is conceptualized in a detailed logic model shown in **Figure 1.** The logic model shows our resources and inputs into the program, the activities and participation and the outcomes and impacts anticipated from the KL2 Program. Shown below in **Table E** are the key metrics used as evidence of success for process measurement (inputs and outputs of the program) and short- , medium-, and long-term outcomes of the program. Each metric or indicator has one or more sources of data, designated with red superscripts, which are shown in the footnotes**.**

Table E. Selected *Key* Metrics (evidence to evaluate the effectiveness of the KL2 program)

Resources/ Inputs	Activities	Results/Outcomes/Impact		
		Short-term	Intermediate	Long-term
[1,4,6,7,8]Mentor publication, training, and funding record Participating departments and programs Participating institutions Program budget Team Science Education [E] Diversity Plan [A,G]	[3]Applications to program [1]Annual KL2 Selection Meeting [1,2]Scholars recruited to program [1,2]URM applicants and entering scholars [5]Courses taught [1,2]CDPs reviewed & updated annually [13]Diversity climate	[4]Clinical competencies obtained (CRAI survey) [1,5]URM complete KL2 program [F,G] [13]Improved diversity climate [4,6,10,11,12] # Publications[D] [10] # Research presentations [4,14] Course completion & program feedback [4] Mentoring effectiveness	[9,10] Faculty or leadership positions[B] [6,10,11,12] # Publications[D] [7, 8,10] Grant funding obtained[B] [2] ↑ Interdisciplinary collaboration	[9,10] Faculty or other research positions[B] [7,8,10,12]Grants[C] [6,10,11,12] ↑ Publications/ citations[D] [10] # Patents [9,10] Leadership accomplishments

Data Sources

[1] Program database, [2]Spreadsheets with Scholar rosters, demographics,[3]Application data (Webgrants), [4]Scholar & mentor surveys (Redcap Survey), [5]University Registrar,[6]PubMed, [7]NIH Reporter,[8]University Grants and Contracts database, [9]LinkedIn, Internet searches, CVs,[10]KL2 Scholar Tracking system (GTSS),[11]My NCBI (My Bibliography), [12]Elsevier Pure (formerly SciVal) Reporting Module, [13]Diversity Climate Survey, [14]Course Evaluations

NCATS Common Metrics (finalized and proposed) for Workforce Development

[A] New educational innovations,
[B] Sustainable careers in CTR,
[C] Percentage of grants,
[D] Scholar publications,
[E] Team science education,
[F] Representation of URM & women,
[G] Innovative processes targeted to URM

Dr. Pelfrey serves as the program manager of the NCATS Common Metrics implementation at the CTSC. We are integrally involved in the NCATS Common Metrics project and have integrated the Common Metrics into our logic model and key metrics/indicators. These are noted in blue post-superscript letters and are listed in the accompanying footnotes. In evaluating our KL2 Program, we administer measures established in collaboration

with the National Education Evaluation Tracking Workgroup and administer specific instruments on a schedule to provide leadership with the timeliest feedback (**Table F**).

Table F: Timing of administration of evaluation instruments in KL2 program

Assessment Measure	Baseline	Annually	At Exit	Post-Grad
Clinical Research Appraisal Inventory (CRAI)[2]				
Career Development Plan (CDP)[3]				
Mentoring Profile Questionnaire & Outcome Measures (MPQ)[4]				
Mentorship Effectiveness Scale (MES)[5]				
Satisfaction Program Exit Interview (SPEI)[7]				
Satisfaction with Program Components (SPC)[8]				
Graduate Tracking Survey System (GTSS)[9]				
Annual Mentor Evaluation of Scholars[10]				
Annual Scholar Evaluation of Mentors				

[2]CRAI: 92-item clinical research efficacy rating scale assessing confidence in 10-domains (Mullikin, 2007, Lipira 2010, Robinson 2013, Eller 2014).(18-20)

[3]CCD: assesses scholars' plans in 4 domains: objectives, methods, research, time line (Horwitz, 2011).(22)

[4]MPQ: 15-item questionnaire assessing the nature of the mentoring relationship & outcomes (Berk, 2005).(27)

[5]MES: 11-items assessing scholars' perceived effectiveness of their mentors (Berk, 2005).(27)

[7]SPEI: 4-question interview protocol with numerous probes assessing satisfaction with the KL2 program.

[8]SPC: 30-items assessing satisfaction with program components (Interdisciplinary Clinical Research Career Development (MCRCD) survey designed by K-12 Evaluators, 2005)

[9]GTSS: Rockefeller University CTSA-based tracking system for trainees (customized to the CTSC). This survey tracks publications, grants, patents and clinical trials as well as several other career outcomes annually (Romanick, 2015)(28)

[10]Annual Mentor Evaluation of Scholars: 36-item survey measuring the scholar's clinical research competencies; narrative evaluation of progress, accomplishments, independence and time commitments. (Adapted from Miller, 1990.)(29)

[11] Annual Scholar Evaluation of Mentors (mentoring competency assessment)(30)

Dr. Pelfrey administers annual surveys to mentors to identify whether scholars are advancing in the skills and competencies of C/T research and to provide scholars feedback. She tracks accomplishments of participants in the KL2 program before, during, and after participation in the program, and collects information and provides feedback regularly on various elements of the programs. Participants complete online anonymous surveys which are reported complete with verbatim comments to faculty and program leadership. Program leadership reviews and discusses the feedback and makes changes in response to this feedback. We have a sound track record for making real-time changes in the KL2 Program in response to scholar feedback (**Table G**).

Table G. KL2 Evaluation feedback and resulting program improvements

Content Area	Scholar Feedback	KL2 Changes Made
Coursework	• More skills in grantsmanship • More flexibility to tailor curriculum • Too much coursework • Addition of specific topics into curriculum: NIH grant style specific aims; mass media for dissemination • Shorten entrepreneur course • Allow access to unique skill development/mentoring opportunities for individual Scholars	• KL2 Selection Study Section reviewers • Unique educational opportunities • Revamped grantwriting course (CRSP 412) to focus on NIH style specific aims and significance/innovation sections • Modified communication course (CRSP 413) to include dissemination through mass media, working with journalists. • Streamlined Innovation & Entrepreneurship course (CRSP 503) into 2-day intensive format • Addition of specific topics into seminar series (below) • Added 'dream mentoring' and similar options to enable scholars to obtain skills in specific areas.
Seminar Series	• Shorter talks and more experts on grantsmanship, better guidelines, feedback on presenting	• Instructions for seminar presentations • Candid feedback • Elevator speeches
Team Science & Networking	• Create more informal opportunities to network	• LinkedIn Group • KL2 Alumni Reunion
Career Development Plan	• Feedback on CDP should be kept constructive; delivered in-person	• Clinical Research Appraisal Inventory • Career Development Plan instructions • 2nd KL2 alumnus on mentorship committee • Feedback regarding CDP
Tracking Career Success	• CV data too voluminous to enter into survey	• Instituted GTSS to track career progress & success

The KL2 evaluation plan utilizes a mixed-methods approach and focuses on traditional metrics of career development at the scholar and mentor level, on the success of the program as a whole, and on the success of the new initiatives (see **Table H**). The metrics and measures will be reviewed at least annually to determine if they are meeting the needs of Dr. Dweik and the KL2 Steering Committee. Any national metrics developed by NCATS will be incorporated into the evaluation plan as they become available.

Table H. KL2 Program domains, data/metrics for measurement and how the data are used for evaluation.

Domain	Data/Measure	Use of Data
Scholars and Mentors		
Scholar selection	• Applications to KL2 program • Feedback from selection meeting	• Monitor demographics, disciplines and URM to ensure diversity in program • Improve selection meeting
Scholar/mentor relationships	• Tracking CDP • Evaluation of mentors by Scholars (Mentorship Profile Questionnaire & Outcomes Measure and the Mentorship Effectiveness Scale) • Mentor evaluation of scholars competencies • Notes from mentoring meeting with Dr. Dweik	• Annual review & reflection to monitor progress on career plan • Measuring the scholar's clinical research competencies; narrative evaluation of progress, accomplishments, independence and time commitments • Assess functioning of mentor-mentee match
Scholar Career Development	• Knowledge & skills acquired (CDP tracking) • Publications/presentations • Grants (applications and awards) • Team participation/collaboration (publications)	• Monitor progression of change in strength/focus areas • Satisfactory progression of clinical research self-efficacy • Determine K-to-R transition, grant success • Assess interdisciplinary collaboration • Identify areas for future development
Career success	• GTSS: annual progress in degree completion, publications, grants, patents, clinical trials, promotions, honors, presentations & changes in leadership roles	• Assess scholar success in developing into productive CT scientists
Use of CTSC resources by Scholars	• Pilot applications from Scholars • Use of Request Management System (RMS)	• Determine if scholars are adequately using CTSC resources
Scholar diversity	• Disciplines, institutions, colleges, and departments of applicants • Ethnicity, race and gender	• Ensure interdisciplinary nature of KL2 program in both faculty and scholars • Ensure representation of URM
Overall Program Evaluation		
Coursework	• Course quality, content, relevance, & satisfaction via end-of-course survey	• Timely CQI changes in course content, instructors
Overall Program	• Exit interviews & Satisfaction with program components survey	• Timely CQI changes to improve program
New Initiatives		
K-Club	• Attendance (KL2, individual K, TL1 trainees) • Feedback from attendees	• Asses value to attendees
Mentor education KL2 graduates	• # Scholars in mentor training • Scholars feedback re: training	• Usage & value of mentor education

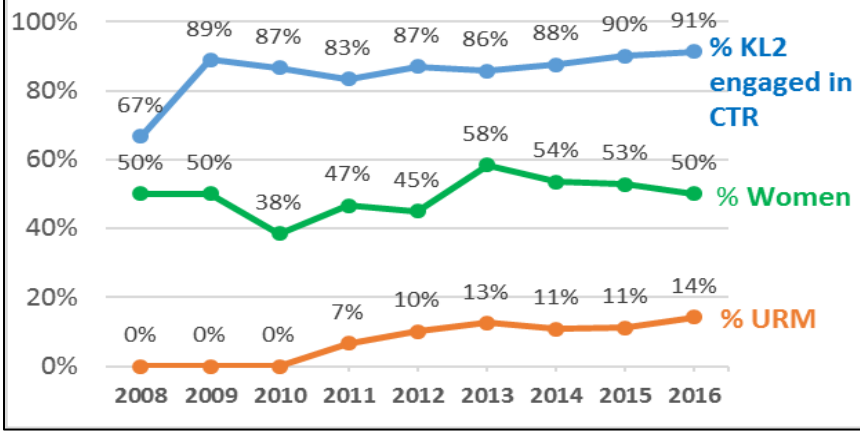
NCATS Common Metrics Results

The NCATS Common Metrics results suggest that our program is highly effective at preparing scholars for careers in clinical and translational research (CTR). Examining the KL2 graduates for the period 2012-2015, there were 21/22 (95%) involved in CTR, and of these, 10% were underrepresented minorities (URM) and 52% were women (Table I). This compares closely with the overall numbers from all KL2 graduates since the inception of the CTSC in 2007, where 91% are engaged in CTR, 12% are from URM and 50% are women (Table I). In Figure. 3, the percent of URM has been steadily rising from 0% URM in 2010 to the 14% in 2016, which is above the 2015 Ohio census demographics for African Americans (12.7%) and Latinos (3.6%) (REF).

Table I. Overall cumulative data for KL2 Careers Common Metric

Metric descriptions	2008-16 graduates	2012-15 graduates
# of KL2 graduates currently engaged in CTR	42/46	21/22
% of KL2 graduates currently engaged in CTR	91%	95%
KL2 grads engaged in CTR, the # of URM	5/42	2/21
KL2 grads engaged in CTR, the % of URM	12%	10%
KL2 grads engaged in CTR, the # of women	21/42	11/21
KL2 grads engaged in CTR, the % of women	50%	52%

Fig. 3. KL2 Graduates Engaged in CTR: 2008-2016



CANDIDATES/SCHOLARS: RECRUITMENT AND RETENTION

The current KL2 program has been fortunate to attract a diverse and very talented pool of applicants. Over the past 12 years, we received 353 (average around 29/year) completed applications **(Table J)** including **48% females**, **13% individuals from under-represented minorities** (of those whose race/ethnicity was known), 35% non-MDs, 49% below the rank of Assistant Professor and 8% individuals from outside the collaborating institutions. This large and varied applicant pool guarantees that the new KL2 program can enroll a talented group of young investigators dedicated to multidisciplinary clinical and translational research careers. The applicants that were selected to become KL2 scholars reflected the applicant pool in diversity and included: 48% females, 13% individuals from under-represented minorities, 48% non-MDs, 56% below the rank of Assistant Professor and 6% individuals from outside the collaborating institutions (**Table K**).

Table J: K12 and KL2 applicants over the past 12 years

Recruitment Year	# of Applicants	# Selected
2004	58 applicants	8
2005	40 applicants	5
2006	44 applicants	5
2007	29 applicants	6
2008	26 applicants	5
2009	29 applicants	4
2010	19 applicants	4
2011	16 applicants	5
2012	28 applicants	8
2013	17 submitted	4
2014	28 submitted	4
2015	19 submitted	5

Qualifications of pool of candidates including types of prior clinical and research training required: Applicants must have a terminal medical degree (e.g. MD, DDS, DNP, PharmD) or a PhD. or PsyD, etc. Individuals from a variety of disciplines are encouraged to apply; e.g., biostatisticians, epidemiologists, behavioral scientists, biomedical engineers, and nurses. All applicants must have evidence of strong academic achievement and scholarship, as well as personal attributes such as high motivation and leadership potential. Further, applicants must be US citizens, non-citizen nationals, or lawfully admitted for permanent residence. Successful applicants have evidence of ability to commit 75% of full-time professional effort to this Career Development Program and its related research activities. A letter of support from the department chairman is required to accompany the application. For candidates in surgical specialties, we do follow the NIH policy and allow a 50% time-commitment but we have generally successfully negotiated with the chairs a time commitment between 50% and 75%.

Table K					
CTSC collaborating institution		**Demographics**		**Terminal Degree**	
CCF	21 (33%)	Female	48%	MD	24 (38%)
CWRU	19 (30%)	Male	52%	MD, PhD	10 (16%)
MHMC	8 (13%)	Asian	19%	DO, PhD	1 (1.5%)
UHCMC	13 (21%)	Bl/Af Am	6%	PhD	27 (43%)
VA	2 (3%)	Hispanic	6%	DDS	1 (1.5%)

Career level required for the program: The award is intended for individuals at a relatively early stage of training (e.g. just after the PhD degree, during, or immediately following a clinical fellowship, or within the first year or two of an initial faculty appointment). The award is meant to stimulate development of outstanding CTS research; therefore, competitive applications must explain how the applicant's research development will benefit from a multidisciplinary approach. If an applicant is already in the process of applying for an independent mentored career development grant, they may be too senior for this program. Candidates should have exposure to clinical research, but not be too advanced to benefit from the KL2 program offerings. It is also crucial that an applicant have sufficient time remaining in their career to apply the skills they develop and to contribute their knowledge to advance science.

Recruitment: A recruitment plan is essential to reach a highly capable and diverse group of scholars. The process starts shortly after the early winter scholar selection. Given the strong and diverse programs in the Cleveland area and associated with Case Western Reserve University, we expect to be successful in meeting our recruitment goals. Specific student groups, organizations and associations are also targeted to specifically reach underrepresented minority groups across both our collaborative institutions and the country. A variety of methods are used to solicit applications and encourage interest in this program within Cleveland, the Midwest, and the United States.

1) Direct mailing of a program announcement to all Deans of American schools of Medicine, Nursing, and Social Work and to Chairs of Departments of Anthropology, Sociology, Psychology, Epidemiology, Biostatistics and Directors of major training programs in health services and outcomes research;
2) Personal letters and program announcements to all Department Chairs, Division Chiefs and Fellowship Directors in our five collaborating institutions;
3) A website created for this program with detailed information about all aspects of the program (casemed.case.edu/ctsc/education/kl2/)
4) Direct mailings to funded investigators from IRB lists of ongoing research projects at our five collaborating institutions;
5) Electronic mail announcements to faculty and fellows across our five collaborating institutions;
6) Advertisements in major national publications (e.g., the *New England Journal of Medicine*); and
7) A series of lunchtime recruitment meetings where the Program Director and/or Co-Directors meet with interested junior faculty and fellows and present details of the KL2 Program.

Recruitment lunches are held at least once per year at each collaborating institution. These recruitment seminars are advertised electronically to all faculty.

Nomination and selection process: Scholar consideration and nomination often begins before the formal website opens for recruitment. The KL2 program is used as a recruitment tool to entice junior faculty to accept appointments at our participating institutions. Although selection in to the KL2 is not automatic, our KL2 program has historically been highly successful in transitioning KL2 scholars to independent funding providing another reason to become part of our research community. After all of the informational sessions and one on one

meeting's, departmental meetings, electronic media blasts and conversations, the dedicated KL2 website sees an increase in traffic.

Application policies and process:

- Applicants must hold a doctorate degree in a health-related discipline or in a discipline otherwise related to the Clinical and Translational Sciences. All applicants must have evidence of strong academic achievement and scholarship, as well as personal attributes such as high motivation. Given our local environment and existing research programs, it is anticipated that we will have applications from many disciplines including but not limited to: CR scholars who are physicians, nurses, applied social scientists, dentists, biomedical engineers, epidemiologists/biostatisticians, anthropologists, psychologists, and sociologists.
- To apply, applicants will use portions of the PHS Form 398, introducing the CR Scholar to the procedures and forms used by NIH. The application will follow a similar format as specified for many NIH K awards, adopting similar page limitations, information requirements on candidate, letters of support, and foundational aspects of the career plan. Applicants will be encouraged but not required to have an identified mentor(s).

The application includes:

1. Three letters of recommendation. One letter must be from the department head. If the applicant is not currently affiliated with one of the five partner institutions, a letter from the prospective department chair indicating their support is required. All letters must address the following criteria:
    - Applicant's demonstrated ability or potential to conduct clinical research
    - Importance of applicant's area of research for the field
    - Multi-disciplinarily of applicant's research interest
    - Applicant's leadership potential
    - Applicant's ability to work in a team-based environment
    - Applicant's 'mentorability'

The Department Chair's letter must also indicate his or her commitment to: 1) support an appropriate department appointment or "academic home," 25% salary support (50% for surgeons) (cost share above $80K); and 2) provide 75% protected time (50% for surgeons) for the prospective scholar to comply with grant requirements.

As part of the application form, the applicant will be asked to list their references' names and e-mail addresses on the ***Letter of Recommendation*** *forms*. Once this information is provided, references will be contacted electronically with instructions for submitting their letters directly to us. Paper submissions will not be accepted.

2. A CV of no more than four pages including the following information in this order:
    - Personal details - name and title, address, phone number(s) and e-mail address
    - Academic background - include: dates of attendance, discipline, degree received and institution for each
    - Postdoctoral training - include dates, field of research, place and title (if applicable)
    - Professional licenses/certificates
    - Academic appointments - include dates, title, department and institution for each
    - Hospital/clinical appointments - include dates, title, and hospital for each
    - Other professional experience - include dates, title and institution/company for each
    - Honors and awards
    - Research/Scholarly Activities - include only the following:
        - Published articles arranged as follows: First-authored; Other publications; In press articles
        - Books and book chapters
        - Peer reviewed conference presentations
        - Do not include work-in-progress or works currently under submission unless they have been accepted for publication, in which case list the journal in which they will appear and "in press"

3. A **one-page** personal statement addressing the following points **(maximum of one page):**
    - Who are you? Why have you chosen a research career?
    - Your previous research experience?
    - How you believe this program will change the trajectory of your career or enhance your movement towards your goals
    - Why you are interested in this particular program, specifically the multidisciplinary aspect of it

4. A **two-page** career development plan addressing the following points **(maximum of two pages):**

- Your five-year goals
- What skills do you need to develop/learn to make yourself a multidisciplinary team researcher?
- Where are the gaps in your knowledge that this program will help fill?
- How will you fill those gaps?
- Be as specific as possible (e.g., courses, workshops, individualized knowledge/skills needed from an expert)
- Include a list of possible research mentors. See attached list KL2 Mentor List (PDF document) for suggestions. Mentors do NOT need to be on this list.

5. A six-page research plan, including the following sections (**maximum of six pages**):
   - Specific aims and hypothesis (one page)
   - Background and significance (one page)
   - Research design and methods (four pages)

6. Literature cited (**one page**)

7. Format for personal statement, career development plan and research plan: Applications use standard NIH formatting.

The process of selection follows NIH study section guidelines. Applications will be reviewed for completeness and responsiveness by the administrator for this Program. Incomplete applications will be returned to the applicant. Applications that are complete will be evaluated for scientific and technical merit during an annual meeting of the Selection Committee, which will be held no later than December 15th. As part of the initial merit review, all applications will receive a written critique and will be scored on a 1-9 scale as is the custom at the Center for Scientific Review at NIH. Each application will receive a minimum of three written critiques of which two will be performed by reviewers from a different discipline than the applicant. Scholars, who are in their third and fourth years, function as tertiary reviewers. Reviewers will consider the following factors:

- The Applicant
  - Is there evidence for an enduring commitment to research?
  - Can the applicant plan and execute?
  - Can the applicant articulate their goals, development plans, and research plans?
  - Does the applicant write well and extensively?
  - Can you envision this applicant as a National leader in their research arena?
- The Research
  - Is the applicant proposing multidisciplinary research? Is the explanation specific?
  - Is the research important? If the research is successful, will it impact human health?
  - Is it likely to lead to a funded research career?
  - Are the ideas well formulated even if the applicant has minimal research experience?
  - Is the research patient oriented? (NIH Definition)
- The Career Plan
  - Does the applicant explain the need for development, and is the explanation compelling?
- Environment and Mentor
  - Does the department chair explicitly state the department's support for the applicant?
  - If a mentor is named, how strong is the mentor and the environment?
  - Does the mentor seem to really know the applicant and the proposal?

Table L. Timing of Submission and Review

7/1/20XX	Website opens for applicants
10/12/20XX	Website closes to applicants
10/13/20XX-10/19/20XX	CTSC KL2 Steering Committee members declare Conflict of Interest (COI)
10/21/20XX	Reviewers Notified of Assignments (Use 1-9 Scale & Note: Reviews are provided de-identified to applicants)
11/2/20XX	Reviews DUE (via WebGrants)
11/16/20XX	CTSC KL2 Steering Committee Selection Meeting

Timing of Submission and Review (Table L)

1. There will be a fall annual deadline for applications.

2. Review of applications will commence after COI (conflict of interest) is declared and within 2 weeks of the deadline.
3. The review meeting will be held by approximately December 15th.
4. Final selection will occur during an Executive Committee meeting within a few weeks.
5. Selected Scholars will be announced in late December/early January for a start the following July.

After applicants have been selected, the Program Director will meet with each scholar individually to provide an in person overview of the program as well as address any questions the scholar might have. The scholars then meet with prospective mentors. Once their mentor team is finalized, each scholar meets with the Director of Curriculum. At this meeting, which mentors are encouraged to attend, a plan for each scholar's planned program of study is outlined. A formal draft is due the Fall after the scholar matriculates into the KL2.

Re-Appointment: Scholars are monitored closely throughout their tenure in the KL2. Each year, they are evaluated by their mentors at several points. Mentors must provide insight and a review of the scholar's submitted research project and budget prior to it being funded. They also must provide a written review, a portion of which is included for submission in the NIH APR. Lastly, each mentor is expected to provide feedback related to their scholar's career development plan. Progress in their academic endeavors and attendance and participation at the noncredit multidisciplinary scholar seminar is also required and tracked. If, at any time, a scholar is not deemed to be making progress, the mentorship committee will discuss next steps. Often, these start with a conversation and plan, involving both the mentor team and scholar. At follow up, if the scholar is not back on track, further planning or decisions are made at that time.

DIVERSITY AND INCLUSION PLAN

A major goal of our training program is to build research teams capable of discoveries, breakthroughs, and innovation. Data indicate that diversity in teams enhances creativity, encourages the search for novel information and perspectives, and leads to better decision-making and problem-solving.[31] According to the 2014 NIH Physician-Scientist Workforce Working Group Report,[32] there are considerable deficiencies in the racial and gender diversity of the clinician-scientist workforce in that the representation of URM and women in the biomedical research workforce falls short of mirroring the US population. Although recruitment and retention of URM and women in the Cleveland CTSC postdoctoral training programs have been comparable to the national average, we believe it is now time to create initiatives to "move the needle" on the otherwise stagnant recruitment and retention of URM and women in research training programs. Given the substantial programming that Case Western Reserve University already has in place to address the pipeline problem of URM and women who are not adequately prepared for science careers at the junior high and high school levels (STEM projects) and at the undergraduate level (Bridges to the Doctorate), we have decided to focus our diversity and inclusion initiatives at the doctoral and postdoctoral research training level. Below we outline our Seven-Point Diversity and Inclusion Plan that is straightforward and realistic which we believe will increase the racial/ethnic and gender diversity of our postdoctoral training programs. We know that achieving diversity and inclusion is hard to accomplish; however, we are committed to engaging in a set of best practices for recruitment and retention of URM and women as outlined in this plan.

Goals and activities of Seven-Point Diversity and Inclusion Plan:

1. **Develop and seek the opinions of a Research Training Diversity Advisory Committee.** We will appoint a Research Training Diversity Advisory Committee to provide consultation and advice to the Diversity Committee of the KL2 program. This Diversity Advisory Committee will consist of eight to ten members (two to three members representing current and past KL2 minority scholars, two mentors/advisors of K or T32 postdoctoral scholars, 2 community members, and a representative of the Office of Diversity at Case Western Reserve University). The Diversity Advisory Committee will meet twice annually with members of the KL2 Diversity Committee to develop and review program recruitment strategies and marketing materials targeted to URM and women. The advisory committee will also review data on the progress toward increasing the number of URM and women in the postdoctoral training programs and review and comment on the results of the annual Diversity Climate Survey (see #7 below).
2. **Develop a data base to track over time the number and progress of URM and women recruited and retained in the program**. We will systematically collect and review data regarding the race/ethnicity and

gender of our trainee candidate pools, our selected candidates, and their career paths during and following the training period. These data will be compared across all racial/ethnic groups and genders. The Diversity Committee, the Advisory Committee and the KL2 Executive will annually review progress toward the goal of increasing the diversity of the program trainees and the success of the marketing strategies.

3. **Develop a Diversity Grant Writing Rapid Response Team to respond to NIH calls for grants addressing diversity in the research workforce**. The NIH has announced that it will be issuing a set of RFAs addressing strategies to enhance diversity in the physician-scientist workforce (RFI November 2015, NOT-OD-16-027). In this Request For Information from NIH, ideas are currently being sought from the research community regarding unique trajectories, potential systematic or structural barriers, and successful strategies to enhance the diversity of the clinician-researcher workforce. We will develop a Diversity Grant Writing Rapid Response Team that is nimble and can respond efficiently to these RFAs when they are released over the next several years. We will assemble a set of KL2 faculty veteran grant writers and members of our Diversity Committee and Diversity Advisory Committee who can develop grant applications using a set of "shelf-ready" ideas that we would like to initiate and test to increase diversity of the clinician-scientist workforce.

4. **Develop recruitment materials and strategies that are specific to different racial, ethnic and gender groups**. Marketing to minority groups must be culturally-specific. With assistance from our Research Training Diversity Advisory Committee, in collaboration with our Marketing Department, we will develop recruitment flyers and materials that are specific to Hispanic, African American, Native American, and female audiences. We currently have a set of strategies in place regarding advertising in specialty journals and at meetings of national organizations. The use of marketing materials that are directed toward specific cultural groups will enhance our current approaches.

5. **Provide peer coaching for trainees recruited into the program**. High-quality mentoring from peers is a demonstrated, evidence-based strategy for improving trainees' persistence and retention irrespective of racial background. A peer coaching program will be initiated in which relationships between more advanced URM and women trainees and those who are in the first and second year of study will be facilitated. Such relationships provide emotional and academic support. Peer coaches help trainees adjust to the demands of their program and the dual demands experienced by UDM trainees. Of equal importance, peer coaches (often referred to as peer mentors) can help reduce the sense of isolation and "otherness" which place students at risk. Since our KL2 program has a system of two mentors, the peer coach may or may not be one of the trainee mentors.

6. **Provide diversity training to all training program mentors**. To improve a training climate related to inclusion, we will provide curricular offerings to support cross-cultural understanding and skill in working with diverse individuals and groups to all training program mentors. We will collaborate with University and Institutional Offices of Diversity in the design and conduct of the diversity training programs. An example of such a program is the *Diversity 360 Program* developed at CWRU by the Office of Inclusion and Diversity. The Diversity 360 Program involves three hours of comprehensive training designed to participants with a deeper understanding of the importance and impact of diversity and to demonstrate how bias, privilege and micro-aggressions negatively affect individuals and the training culture. It also provides ways for participants to become change agents and diversity champions with new knowledge, ideas and resources about best practices for enhancing diversity and inclusion.

7. **Implement a Diversity Climate Survey annually among the K program mentors and trainees**. A Diversity Climate Survey will be deployed biannually among the postdoctoral trainees and mentors. The CWRU Office of Inclusion and Diversity currently conduct such a survey, but the results have not been systematically collected and analyzed for postdoctoral trainees and the research workforce. Data from this survey will enable a baseline assessment and an assessment of the impact of several of the strategies in our Seven-Point Diversity and Inclusion Plan. The results of the survey will be reviewed by the Diversity Committee, the Training Diversity Advisory Committee, and the KL2 Executive Committee and viewed as an indicator of progress toward diversity and to identify areas for improvement.

2. TL1 Research Training Program Plan: Clinical and Translational Scientist Training Program (CTSTP)

2.1. Mission and objectives

Mission: Our mission is to develop a C/T workforce that will enable research to address unmet health needs with efficiency, effectiveness and excellence. We aim to produce future leaders in C/T research by providing rigorous and effective C/T research training across disciplines, spanning predoctoral to postdoctoral training.

Aims: We will provide training in C/T research that encompasses a broad range of scientific disciplines. Core CTSTP training activities (some shared with the KL2) will include training in team science and interdisciplinary research, and professional and leadership development. Fig. 1 provides a schematic of the predoctoral and postdoctoral training programs and their elements.

Aim 1: Implement novel models for predoctoral combined degree training in C/T research: A) Develop MD-PhD training in recently launched CTSTP predoctoral programs (C/T Science, Systems Biology and Bioinformatics) and other relevant PhD programs. B) Train leading nurse-scientists in our recently launched DNP-PhD program.

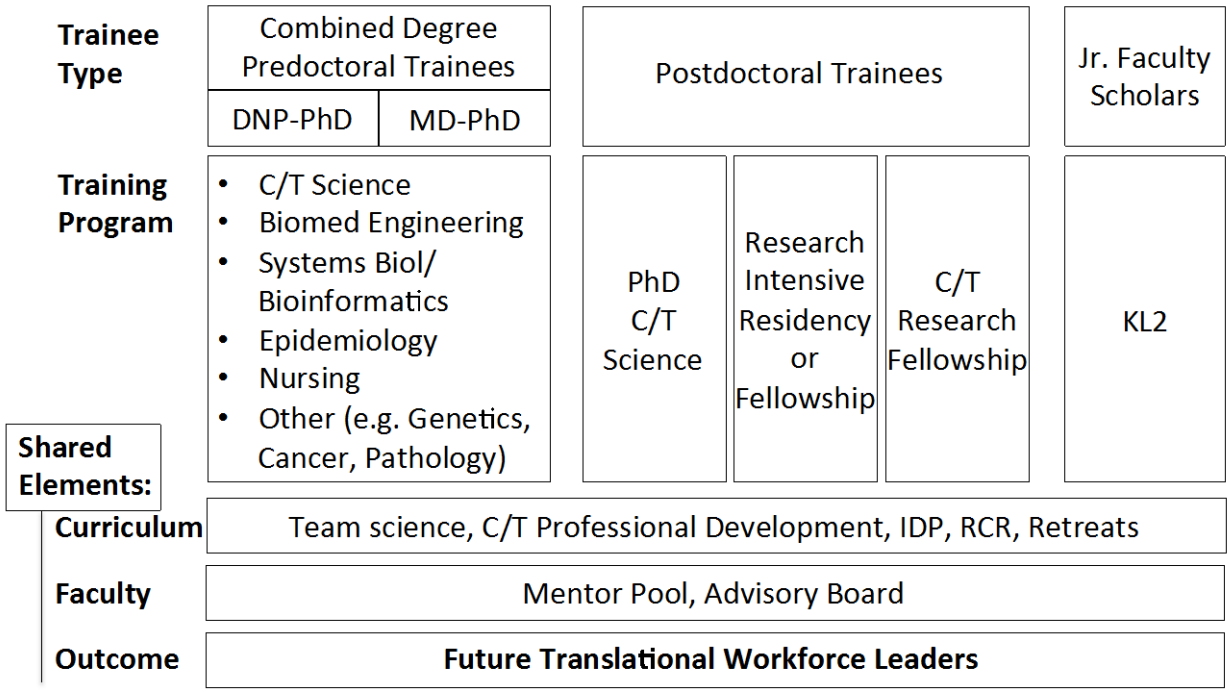
Aim 2: Launch novel programs for postdoctoral C/T research training through three new training paths: A) Trainees enter our PhD program in C/T Science with a prior clinical doctoral degree (or a relevant MS degree; the latter are actually predoctoral trainees but will follow the same curriculum as postdoctoral C/T Science trainees). B) Research-track residencies/fellowships in C/T fields. C) C/T research fellowships that will develop strong junior C/T scientist candidates (e.g. physicians, nurses and dentists) to the point where they can apply for career development awards or research grants (e.g. K08, K12, KL2, other).

Abbreviations and Definitions

CTSTP: Clinical and Translational Scientist Training Program (this TL1 training program)
C/T: Clinical/Translational
CWRU: Case Western Reserve University
CTSC: Clinical and Translational Science Collaborative (CWRU CTSA program)
SOM: School of Medicine
SOE: School of Engineering
SON: Frances Payne Bolton School of Nursing
CC: Cleveland Clinic
UHCMC: University Hospitals Cleveland Medical Center
VAMC: Louis Stokes Cleveland Veteran's Administration Medical Center
MHMC: MetroHealth Medical Center
"University Program", four-year MD program provided at CWRU SOM
CCLCM: Four-year research-intensive MD program provided by Cleveland Clinic Lerner College of Medicine of CWRU
TWD: Translational Workforce Development
RCR: Responsible Conduct of Research
TGE: Training Grant Eligible
URM: Underrepresented Minority
CRSP: Clinical Research Scholars Program (MS program)
BME: Biomedical Engineering

Tables NIH format training grant tables are numbered; additional tables with letter designations are embedded below. Tables report prior academic year data through June 30, 2016 or current status as of April 2017.

Figure 1: CTSC Research Education Programs Schematic



2.2. Rationale and overview of proposed program

Rationale and need: Clinical/translational (C/T) scientists are increasingly important for cutting edge biomedical research that achieves "bench to bedside to curbside" impact to address unmet health needs. To address these needs, translational workforce development (TWD) is needed to train C/T scientists with new skill sets. These skills will enable them to develop innovative strategies to address unmet health needs with effectiveness, efficiency and economy. Critical factors for success will be skills for interdisciplinary work, ability to work across the spectrum of laboratory science to clinical and public health research, and the ability to envision and design implementation of advances in clinical and community settings. To address these needs, the CWRU CTSTP will support C/T research training in both predoctoral and postdoctoral phases. These programs will be coordinated with our KL2 program to share training in team science, professional development activities and mentorship models. Together, these programs will provide a complete pipeline for training and development of C/T scientists.

2.3. Institutional qualifications, participating departments

2.3.1. Institutional resources: Participating institutions include CWRU, CC, UHCMC, MHMC and VAMC. These sites have outstanding resources for cutting edge C/T research. CWRU SOM is a top tier research-intensive medical school, ranking 25th among some 140 U.S. medical schools in research (US News and World Reports, 2016 and 2017). CWRU and its affiliates garnered over $275M in NIH research funding in FY16. The SON is research-intensive, ranking 14th in the U.S. for NIH funding among schools of nursing (FY16) and 8th for DNP training (US News and World Reports, 2017). The SOE has over $40M in research expenditures. The Department of Biomedical Engineering, a joint department of the SOM and SOE, is ranked 15th by US News and World Reports (2017). Each year, CWRU SOM training programs include a total of approximately 100 MD-PhD students, 760 MD students, 430 PhD students, 590 MS students, 60 MPH students and 40 MA students. Clinical programs provide critical resources for training and research at CC (1268 beds), UHCMC (771 beds), MHMC (708 beds) and VAMC (586 beds). ACGME-accredited slots number 740 residents and 321 fellows at CC, 675 residents and 194 fellows at UHCMC, 308 residents and 56 fellows at MHMC. The VAMC has a total of 148 slots that are staffed by residents participating in residency or fellowship programs based at UHCMC, CC or MHMC. Numerous interdepartmental centers provide resources to promote research, training and collaboration among faculty members with different research backgrounds. Prominent examples include the NCI-designated Case Comprehensive Cancer Center, the Center for AIDS Research, AIDS Clinical Trial Unit, Geriatric Research Education and Clinical Center, Mellen Center for Multiple Sclerosis, Skin Diseases Research Center, Tuberculosis Research Unit, Center for Stem Cell and Regenerative Medicine, Center for Proteomics and Bioinformatics, Center for Global Health and Diseases and Visual Sciences Research Center.

2.3.2. Institutional training grants: The TL1 will provide predoctoral and postdoctoral C/T research training to meet the TWD goals of the CTSC. This section describes other training grant resources at CWRU SOM and indicates the unique aspects of the TL1 in supporting C/T research training.

Research training at CWRU is supported by our CTSA (including KL2 and TL1), our NCI-designated Case Comprehensive Cancer Center (with a K12 program) and NIH training grants. Of NIH-supported training grants, 27 include CTSTP mentors and support a total of 85 predoctoral and 60 postdoctoral positions (Table 3). These programs provide a rich set of resources and community for research training, yet the TL1 is unique among them in supporting the breadth and type of C/T research training proposed in this application. The TL1 and KL2 are the only training grants to develop key areas of C/T training, such as team science and interdisciplinary research. No other training grant supports the PhD program in C/T Science. No other training grant encompasses the breadth of C/T research within its mission; other grants are focused on specific scientific or disease fields. The CTSTP will be unique in developing an integrated breadth of C/T research training for both predoctoral and postdoctoral training. Of the other training grants, only the MSTP T32 supports research across a broad swath of scientific fields, but the MSTP does not develop C/T research training and is focused on basic biomedical research.

2.3.3. Participating departments indicated in Table 1 include all departments in which participating faculty mentors have primary appointments, including PhD-granting departments, departments with research-intensive residency or fellowship programs, and departments with faculty who will be engaged in training of predoctoral or postdoctoral trainees. The broad scope of the CTSTP includes engagement across many departments. The participating departments house a total of 414 predoctoral and 338 postdoctoral trainees, demonstrating a robust training environment. The 65 CTSTP mentors have a total of 166 predoctoral trainees (121 training grant eligible/TGE, 8 currently supported by this grant with 3 more appointments that will be made for this budget period). The CTSTP mentors have 97 postdoctoral fellows (38 TGE; there are NO TL1 postdoctoral

appointees, as this grant does not currently have postdoctoral slots). This understates the postdoctoral trainee pool, as CWRU does not count research track residents and fellows in postdoctoral fellow counts used for Table 1. Postdoctoral applicant pools are robust and are reported in Table 6B; we will draw from the most competitive subset of these applicants for the TL1 postdoctoral program.

Table A: CTSTP-participating predoctoral training programs	**Current #CTSTP students**
Biomedical Engineering	9
C/T Science (launched 2015)	2
Epidemiology	1
Genetics	4
Immunology	4
Nursing	3
Pathology	4
Systems Biology/Bioinformatics	2
Other	4
Undecided	3
Total	36

#Includes past or current TL1 appointees from table 8A who are currently in PhD programs or are in clinical phase of combined degree training.

URM trainees: 7/36 (19.4%) of the above are URM trainees (4 African-American & 3 Hispanic students).

CTSTP-participating predoctoral programs (Table A): The CTSTP predoctoral program includes MD-PhD and DNP-PhD training in C/T research fields. Participating units include the MD and DNP programs for clinical training and a set of PhD programs (Table A) that focus on clinical and translational research (e.g. C/T Science, Biomedical Engineering, Epidemiology and Biostatistics, Systems Biology and Bioinformatics, Nursing) as well as the subset of students in other PhD programs with C/T research within their scope (e.g. Genetics and Genome Sciences, Pathology). The PhD program in C/T Science was just launched in 2015, so enrollment will increase in this program. It has already enrolled 2 CTSTP MD-PhD and 5 other students who already hold a graduate degree).

Our new PhD program in C/T Science is housed in the Center for Clinical Investigation, which also houses other CTSC functions. Most PhD programs are administratively centered in a department at CWRU, but participation in PhD programs is interdepartmental and includes faculty and trainees in their "home departments" at all affiliates. Trainees are distributed across multiple PhD programs (Table A) and in home departments at all affiliates. Rigorous and unified training expectations are maintained by PhD programs through curricula and programmatic activities that are required of all predoctoral trainees. Importantly, CTSTP trainees will participate in shared TL1/KL2 curricular and programmatic activities (Fig. 1 and section 3.3.3), which will provide a consistent and unified approach to achieve CTSTP training goals.

CTSTP-participating postdoctoral programs: See section 3.3 for other postdoctoral C/T research training pathways (PhD in C/T research, C/T research fellowships). This section describes participating research-intensive residency & fellowship programs that will be sources of TL1 applicants (Table B). All include a minimum of two years of time protected for research with not more than 25% clinical effort. These programs provide distinctive tracks for research-intensive training within the residency or fellowship program for trainees who are committed to a research-intensive career. Most of the training areas in Table B involve more than one participating institution, either by the existence of research intensive programs at more than one site (e.g. FasTrack research pathway Medicine residencies at MHMC and UHCMC/VAMC) or the existence of inter-institutional training programs (e.g. Gastroenterology research fellowship involving CC & UHCMC; Nephrology program involving MHMC, CWRU, UHCMC and VAMC; Medicine residency involving UHCMC/VAMC).

Postdoctoral trainees will participate in activities of their home department, residency or fellowship program, and in core TL1/KL2 training activities (e.g. team science training and professional development activities; Fig. 1 and section 3.3.3). This will insure that the research training goals of the CTSTP are attained.

2.4 Innovative features: CWRU SOM has a rich history of innovative biomedical research training. CWRU has provided integrated, combined-degree MD-PhD training program since 1956 with 303 MD-PhD alumni and 104 current MD-PhD students (2016-2017). Outcomes demonstrate success in research and academia, as 71% of MD-PhD alumni are faculty in medical schools, and 14% work at NIH, at a research foundation or in industrial research (biotech/pharma). In 2004, we were among the first group to receive a Roadmap K12 grant, which was used as the foundation to develop our current KL2 program. The Center for Clinical Investigation was created in 2007 to administer C/T research degree-granting programs, provide academic appointments to C/T investigators at all CTSC partner institutions, and sponsor CTSC-wide special lectures and symposia.

CTSTP innovations and plans: Our CTSTP has driven substantial innovation in C/T research training (Table C). In 2007, Dr. Harding launched the CTSTP as the TL1 component of our CTSC. The strategic focus has been on predoctoral training in combined degree programs, which has enabled substantial progress in development of new PhD programs and combined degree training options. Innovative advances have included the launch of two new PhD programs (C/T Science, launched in 2015, has 5 students with a prior graduate degree plus 2

MD-PhD students; Systems Biology and Bioinformatics, launched in 2011, currently with 8 PhD and 3 MD-PhD students, and 3 PhD graduates). A combined degree DNP-PhD program for training of nurse-scientists was launched in the School of Nursing in 2010 (3 current students, 2 graduates). The DNP-PhD program is one of only roughly four such programs in the U.S. Other new opportunities in MD-PhD training in C/T research have been developed under our CTSTP by expanding MD-PhD training in other C/T-related PhD programs, including Epidemiology, Biomedical Engineering, and selected C/T areas of other PhD programs. The CTSTP has become an engine that drives educational innovation, curriculum development, rigorous standards (for academics, student support, admissions, mentoring, and career planning), enhanced ability to recruit top students, enhanced institutional support, cross fertilization and broader inter-institutional collaboration in predoctoral C/T research training, and development of programmatic activities that include interdisciplinary collaboration among different research fields.

Table B: CTSTP-participating Residencies/Fellowships*

Program	Research timing	Years Research#	Research track/total trainees
Research intensive residencies			
Dermatology	PGY3-4	2	3/19
Medicine	PGY3-5	3	8/196
Pathology	PGY3-4	2	1/23
Research intensive fellowships			
Gastroenterology	Yrs 1-2	2	4/27
Infectious Diseases	Yrs 2-3	2	2/8
Pediatric Heme-Onc,	Yrs 2-3	2	6/6
Nephrology	≥2 yrs	2	1-2/6

*T32 support: Among the residencies, only Dermatology has T32 support; the fellowships have T32 support except Pediatric Heme-Onc. The TL1 will be the only NRSA support for many training positions above.
#Years with ≤25% clinical time.

Future plans: We will continue to develop the recently launched predoctoral programs, but we are now also ready to launch new postdoctoral research training programs. These will include three major training paths and trainee groups: 1) PhD program in C/T Science for postdoctoral trainees (or trainees with a prior relevant MS degree; these are actually predoctoral trainees but will follow the same curriculum as postdoctoral C/T Science trainees). 2) Postdoctoral C/T research fellowships that will develop strong junior C/T scientist candidates (e.g. physicians, nurses and dentists) to the point where they are competitive for K, research or other awards; 3) Research-intensive residency and fellowship programs that will develop C/T physician-scientists.

Collaboration with KL2: We will more closely align the CTSTP/TL1 with our KL2 program to foster interdisciplinary, team-based C/T research training. The TL1 and KL2 will share a mentor pool, advisory board, team science curriculum, research training components, and professional development activities. These activities have been developed for our KL2 program and recently applied to predoctoral trainees; they will now be shared among the TL1 and KL2 programs. Our new goals coupled with our prior innovations in the TL1 and KL2 programs will create a full pipeline of training across predoctoral, postdoctoral and KL2 scholar stages to train successful C/T research leaders.

Medical education and MD-PhD program innovations: CWRU SOM has three major training tracks: the University Program, the CCLCM, and the MD-PhD track (MSTP and CTSTP; these tracks use the University Program MD curriculum with modifications and integration of PhD curriculum components). The University Program has ~170 students/class, including 12-15 MD-PhD students/class. In 2006, CWRU SOM launched the innovative WR2 ("Western Reserve 2") medical curriculum, which includes a research block and research thesis for all MD students. Instruction includes small group problem-based learning as well as lectures and other teaching methods. The WR2 curriculum develops a focus on scientific literature, and small groups use an evidence-based approach with emphasis on interpretation of data from primary literature. Students are asked to identify the research question/hypothesis, evaluate study design, interpret data and critique the authors' interpretation of the data. In 2004 CWRU SOM and CC collaboratively launched the Cleveland

Table C. Novel Training Models: Summary of CTSTP Innovations and Changes

Recently launched:
New PhD program in C/T Science
New PhD program in Systems Biology and Bioinformatics
New DNP-PhD program (one of only ~4 in the U.S.)
Expansion of MD-PhD training into new C/T areas
Proposed:
Postdoctoral C/T PhD training
C/T research fellowships
Research-intensive residency/fellowship
Shared TL1/KL2 curriculum in team science, C/T research, professional development

Clinic Lerner College of Medicine of Case Western Reserve University (CCLCM). The CCLCM provides an innovative five-year MD curriculum with a full year for research (a masters level degree may be integrated). The program has an extensive research curriculum (including curriculum components in research techniques, data analysis, basic research, and clinical research). There are 32 CCLCM students/class, including MD-MS or MD-MPH students. The University Program and CCLCM share the same clinical clerkships and rotations in M3–M4.

3. Program Plan

3.1. Program Administration

Summary of program governance: The Executive Committee is composed of Dr. Harding (Director) and three Associate Directors (Drs. Dweik, Moore and Spilsbury). This group will provide direct program management. These faculty and others will constitute a Steering Committee responsible for program governance. A TWD Advisory Board will provide broad oversight of the program. The Director reports to the CTSC PI (Michael Konstan, MD), the Dean of the School of Medicine (Pamela Davis, MD, PhD), and the TWD Advisory Board. An Administrative Director, Kathryn Schultz, MS, MBA, and two other staff will support program activities and grant management (in collaboration with KL2 and CTSC administrative leadership). Program leadership is drawn from all participating institutions. All program leaders and mentors have faculty appointments at CWRU. The institution of primary appointment/employment is indicated for individuals below (in some cases of balanced function and dual employment, two institutions are indicated).

CTSTP Director: **Clifford V. Harding, MD, PhD** (CWRU SOM/UHCMC) is the Joseph R. Kahn Professor and Chair of Pathology at CWRU and UHCMC. He has a long-standing productive NIH-funded research program on the regulation of immune responses during infection with Mycobacterium tuberculosis (Mtb) or HIV. He has over 190 publications (>10,000 citations, h-index = 55). His main current scientific focus is studying the mechanisms of immune evasion and persistence of infection in tuberculosis. He has been a leader in developing research training for PhD students, MD-PhD students and physician-scientists. He has been the Director of the MSTP at CWRU since 2001. He has served on the Steering Committee and multiple other committees for the AAMC GREAT MD-PhD Section. He has developed both basic and translational research training programs; he has designed and launched new training programs in Immunology and Cancer Biology (e.g. as founding Director of the Immunology Training Program at CWRU). He designed and launched the CTSTP that is the focus of this application and has directed the CTSTP since its launch in 2007. He worked with SON faculty to design the DNP-PhD program, and he contributed substantially to the design and launch of the new C/T Science PhD program (he continues to serve on its Advisory Board.). He has contributed to the national/international research community with service on numerous NIH and international study sections and through the American Association of Immunologists (e.g. as Chair of the AAI Committee on Public Affairs). Dr. Harding has mentored 27 PhD students and 11 postdoctoral fellows (some completed training prior to the reporting period for Tables 2 & 5); those who have completed training have positions as medical school faculty (12), NIH scientists (2), and program leaders in industry (8); others are still in training. Dr. Harding will have 20% effort devoted to the CTSTP. Dr. Harding is highly committed to working personally with trainees; most days he has at least one meeting with a trainee to advise and mentor.

CTSTP Associate Director: **Raed Dweik, MD** (CC) is Director of the KL2 program, Professor of Medicine, CCLCM, CWRU, Director of the Pulmonary Vascular Program, Department of Pulmonary, Allergy, and Critical Care Medicine at CC. His NIH-funded research is focused on the pathobiology of pulmonary hypertension, pulmonary vascular biology, nitric oxide and lung matrix. He contributed to the discovery of low nitric oxide in idiopathic pulmonary arterial hypertension, and he recently discovered dysregulation of hyaluronan production in pulmonary hypertension. Dr. Dweik is a strong proponent of the importance of mentoring and nurturing young researchers in translational research careers. His current and former trainees include KL2, K23 and K99 award recipients. Dr. Dweik will have 20% effort devoted to the CTSC education programs.

CTSTP Associate Director: **Shirley Moore, PhD, RN, FAAN** (CWRU SON) is Professor and Associate Dean for Research in the SON. She is a behavioral scientist and PI of a P30 Center of Excellence in Self-Management Research. Her research addresses self-management of health and behavior change in child and adult populations, particularly health-promoting behaviors of dietary intake, physical activity & weight management. She is an expert in designing and testing interventions for behavior change. She has served as PI of several NIH-funded studies. She is experienced in building multidisciplinary teams of physicians, nurses, biomedical engineers, social workers, exercise physiologists, nutritionists, computer scientists, economists & statisticians. Dr. Moore has three current and five past predoctoral trainees (some graduated before the reporting period for Tables 2 and 5) and two current and five past postdoctoral trainees. Her trainees have

attained NRSA, K01, KL2 and other grants; they include current faculty at 10 universities. Dr. Moore will have 5% effort devoted to CTSC education programs, particularly the TL1/KL2 core curriculum.

CTSTP Associate Director: **James Spilsbury, MPH, PhD** (CWRU SOM) is Assistant Professor of Epidemiology & Biostatistics. He is Co-Director of the PhD program in C/T Science; Chair of the KL2 Curriculum Committee; and Director of the CTSC Academic Development Core, where he manages interdisciplinary educational and training activities. He directs Clinical Research Scholars Program (an MS program) and a graduate certificate program in clinical research. He is a graduate of our KL2 program. Dr. Spilsbury is an anthropologist focused on the effects of social and cultural environment on children's health and well-being. His NIH-funded research investigates effects of neighborhood conditions on child maltreatment. Dr. Spilsbury is strongly committed to mentoring. He has served as the faculty advisor/mentor for numerous students in the MS program, and he has served as a dissertation committee member on doctoral students' committees in C/T Science, Anthropology and Social Work. Dr. Spilsbury will have 10% effort devoted to the CTSC education programs, e.g. his effort for the C/T Science PhD program.

CTSTP Executive Committee:

- Clifford V. Harding, MD, PhD (CTSTP Director, CWRU SOM/UHCMC)
- Raed Dweik, MD (KL2 Director, CTSTP Associate Director, CC)
- James Spilsbury, PhD (CTSTP Associate Director, Co-Director, C/T Science PhD Program, CWRU SOM)
- Shirley Moore, PhD, RN (CTSTP Associate Director, CWRU SON)

The Executive Committee will manage the program to implement the decisions of the Steering Committee and Advisory Board and develop recruitment, curriculum, trainee advising and assessment of the program. Dr. Harding will provide overall leadership. Dr. Dweik will help lead the postdoctoral portion of the CTSTP, complementing his role as KL2 Director. Dr. Spilsbury will contribute particularly with regard to the C/T Science PhD program. Dr. Moore will help oversee the DNP-PhD program and contribute to the CTSTP core curriculum and professional development programs, particularly team science. All Executive Committee members also serve on the Steering Committee.

CTSTP Steering Committee: The Steering Committee will make decisions regarding program policies; curriculum development; program guidelines; trainee selection/admissions; approval of mentors; tracking, evaluation and guidance of current trainees; and other issues facing the CTSTP. Steering Committee members will also individually provide student advising. The committee will track trainee performance, intervene to help when indicated, and make disciplinary decisions when needed, including dismissal from the program. The CTSTP Director will be Chair of the Steering Committee. The Steering Committee contains representatives of all CTSTP programs. Members also include representatives for CTSC outcomes evaluation, SOM MD admissions, and the Associate Dean for Graduate Education. The CTSTP Steering Committee will meet at least monthly in entirety or in subcommittees. The three subcommittees will manage specific areas as indicated below and report to the full Steering Committee during the combined meetings. The full Steering Committee is the combination of the following subcommittees.

Predoctoral MD-PhD subcommittee:

- Clifford V. Harding, MD, PhD (Subcommittee Chair, CTSTP Director, CWRU SOM/UHCMC)
- Derek Abbott, MD, PhD (Pathology, CWRU SOM)
- Eben Alsberg, PhD (Biomedical Engineering, CWRU)
- Dominique Durand, PhD (Biomedical Engineering, CWRU)
- Robert Fairchild, PhD (Organ transplantation research, CC)
- Alex Huang, MD, PhD (Pediatric Hematology/Oncology, UHCMC)
- Debra Leizman, MD (Clinical Tutorial Director, UHCMC)
- James Spilsbury, PhD (CTSTP Associate Director, Co-Director, C/T Science PhD Program, CWRU SOM)
- Cathy Stein, PhD (Epidemiology, CWRU SOM)
- Nicole Steinmetz, PhD (Biomedical Engineering, CWRU)

Predoctoral DNP-PhD subcommittee:

- Jaclene Zauszniewski, RN, PhD (Subcommittee Chair, DNP-PhD Program Director, Nursing, CWRU)
- Clifford Harding, MD, PhD (CTSTP Director, CWRU SOM/UHCMC)
- Shirley Moore, PhD, RN (CTSTP Associate Director, Nursing, CWRU)
- James Spilsbury, PhD (CTSTP Associate Director, Co-Director, C/T Science PhD Program, CWRU SOM)

Postdoctoral subcommittee:

- Clifford V. Harding, MD, PhD (Subcommittee Chair, CTSTP Director, CWRU SOM/UHCMC)
- Derek Abbott, MD, PhD (Pathology, CWRU SOM)
- Raed Dweik, MD (KL2 Director, CTSTP Associate Director, CC)
- Robert Fairchild, PhD (Organ transplantation research, CC)
- Aaron Proweller, MD, PhD (Director, Research track in Medicine, UHCMC)
- John Sedor, MD (MHMC)
- James Spilsbury, PhD (CTSTP Associate Director, Co-Director, C/T Science PhD Program, CWRU SOM)

At-large Steering Committee members:

- Margaret Larkins-Pettigrew, MD, Chair for Clinical Excellence and Diversity (UHCMC)
- Paul MacDonald, PhD, Associate Dean for Graduate Education (CWRU)
- Clara Pelfrey, PhD, Evaluation Director, CTSC (CWRU)

Translational Workforce Development (TWD) Advisory Board: The TWD Advisory Board will meet one to two times per year and as needed to provide high level oversight, advice on the balance of different objectives, review and outcomes assessment for the TL1, KL2 and other TWD aims of the CTSC. This will facilitate coordination and synergies between the KL2 and TL1 programs, and the other CTSC programs with TWD goals.

- Mark Chance, PhD (TWD Advisory Board Chair, CTSC Associate PI, TWD Program Director, CWRU)
- Robert Bonomo, MD (Chief of Medicine VAMC)
- Al Connors, MD (Chair KL2 mentoring committee, MHMC)
- Neal Dawson, MD (Chair, KL2 multidisciplinary training committee, MHMC)
- Serpil Erzurum, MD (CTSC Associate PI, CC)
- Stanton Gerson, MD (Director, Case Comprehensive Cancer Center, CWRU)
- Jonathan Haines, PhD (Chair of Epidemiology and Biostatistics; Director of Informatics, CTSC; CWRU)
- Mukesh Jain, MD (Chief Scientific Officer, UHCMC)
- Robert Kirsch, PhD (Chair, Biomedical Engineering, CWRU)
- Michael Konstan, MD (CTSC PI, CWRU)
- Li Li, MD (Director, C/T Science PhD program, CWRU/UHCMC)
- Mary Kerr, PhD, RN (Dean, School of Nursing, CWRU)
- Anthony Wynshaw-Boris, MD, PhD (Chair of Genetics, CWRU)

Trainee leadership: Trainee leadership is prominent and important to the CTSTP. The MSTP/CTSTP Student Council organizes program events such as MSTP/CTSTP summer and winter retreats (which include both MD-PhD and DNP-PhD students), evening seminar series, recruiting activities (including URM-specific activities), professional development activities (F30 grants workshop, RCR+4 sessions, Women's Mentoring Group, Peer Mentors Program, Community Service Committee), representatives to SOM committees (Faculty Council, Committee on Medical Education, CWRU Graduate Student Senate, SOM Biomedical Graduate Student Organization). The Director meets with Student Council once per month for a dinner working meeting; in addition to the elected leaders of Council, all trainees in the program are invited to attend. Council provides feedback on all aspects of the program and proposes new initiatives. Future plan for postdoctoral trainees: When postdoctoral trainees are added to the program, we plan to develop postdoctoral trainee leadership involvement in a similar manner. This will include sharing of some of the forums described above for predoctoral trainees, and there will be additional activities added relevant to postdoctoral training stages (collaboration with KL2, research track residency groups). Council will collaborate with Drs. Harding and Pelfrey in specific program evaluation efforts.

3.2 Program Faculty

The TL1 and KL2 share a mentor pool and many training functions, providing strong synergy for mentorship in the C/T research-training pipeline, but we do assign mentors to involvement in specific stages of training (predoctoral, postdoctoral, KL2) depending on their training expertise. In the shared mentor pool (Table 2), we have noted next to the mentors' names whether they will be mentors in the TL1 predoctoral ("Pre"), TL1 postdoctoral ("Post") and/or KL2 ("K") program. There are 65 approved primary scientific mentors (Table 2) with faculty appointments in the Schools of Medicine, Nursing and Engineering, and including faculty located at all affiliated hospitals. The participating faculty represent strengths in many areas of C/T research and include physicians, nurses, PhD researchers with C/T research interests, biomedical engineers, informatics faculty, social scientists and others. The mentors are all productive C/T researchers with externally-funded research

programs. Their research areas include those described within the program descriptions (section 3.3.5) and listed in Table 2. The 55 current and graduated CTSTP students have been mentored by 46 of our faculty (3 students are still in process of choosing a mentor). Overall, the participating faculty will support rigorous interdisciplinary research as well as in-depth mentoring in specific areas of research.

Mentor approval and assessment: CTSTP mentors must be approved by the CTSTP Steering Committee. The program will actively develop the mentor pool as new candidates become available. Prospective mentors submit their CV, funding data and training record. The Steering Committee reviews and votes on each application to determine whether to grant approval either as a Senior Mentor (well established research program, NIH funding and training record) or an Initial Mentor (e.g. promising junior faculty members with a more limited training record who are on a strong research trajectory and committed to developing mentoring skills – see Mentor Development, below). Existing mentors are reviewed annually to confirm that criteria for approval are still met. If a mentor does not provide appropriate mentoring, mentor approval will be removed. Assessment will include mentee feedback gathered in a regular ongoing manner. In addition, the requirement for a CTSTP Steering Committee representative on the thesis committee (predocs) or mentoring committee (postdocs) will provide an opportunity for CTSTP leadership to directly observe and assess mentor-mentee interactions and effectiveness of mentoring. If any shortfalls in mentoring are found, additional mentor training will be required.

Criteria for mentor approval include: 1. Strong scientific productivity and leadership of a well-developed independent research program that will allow trainees appropriate access to and "ownership" of cutting-edge research projects. 2. Consistent record of extramural funding as P.I. (NIH R01 grants or equivalent; this may be adjusted for promising new junior faculty with a strong letter of support from their Chair). 3. A track record of successful prior mentorship (may be waived for Initial Mentors, but they must have a Senior Mentor as a Co-Mentor, a strong letter of support from their Chair, and a plan for mentor development).

Mentor development: We will require that all Initial Mentors participate in a Mentor Development Program, and we will strongly encourage Senior Mentors to participate in this program. Mentors will receive training through resources at ctsacentral.org (https://ctsacentral.org/consortium/education-and-training/, e.g. the Mentor Development Programs Course Materials from UCSF). The TL1 and KL2 will develop mentor training forums, including discussion of literature on mentoring (see https://ictr.wisc.edu/MentoringPublicationsReports). An Initial Mentor must have an approved Senior Co-Mentor for any trainee; the Senior Co-Mentor may or may not be a collaborator but he/she must participate actively in advising and oversight of student progress. The Initial Mentors will be guided and mentored in developing their own mentoring skills by the Senior Mentor. These arrangements allow talented junior faculty to participate in the mentor pool and develop their mentoring skills.

Selection of mentors by trainees: Trainees will explore research environments and mentors before selecting their primary scientific mentor. MD-PhD students rotate in different labs during their first 1.5 years. DNP-PhD students have ample opportunity to explore opportunities before the start of their PhD project, e.g. during their research practicum. Postdoctoral fellows will have opportunity to explore potential mentors with guidance from CTSTP advisors and (for residents/fellows) leadership of their research-track residency/fellowship.

Expectations for mentors: Mentors are expected to provide extensive personal mentoring of students for scientific guidance and professional development, including career mentoring. Mentors also provide research facilities and materials. In addition, mentors are expected to take active roles in the CTSTP programmatic events, thesis committees or postdoctoral mentoring committees, recruiting and interviewing activities.

Cross-institutional participation and interactions: CTSTP participating faculty are located in the SOM, SOE, SON, and all CTSC affiliates (CC, UHCMC, MHMC, VAMC). The SOM is adjacent to the rest of the CWRU campus, facilitating collaborations with the SOE and SON. CC, UHCMC and VAMC are all within walking distance of the SOM, and MHMC is only 25 min by car. CTSTP students have been trained at laboratories at CWRU, UHCMC, CC, VAMC and MHMC. The new PhD program in C/T Science has engaged mentors at all affiliated sites, and the seven initial trainees in this program are at SOM (2), CC (1), MHMC (1) and UHCMC (3). Many CTSTP trainees have mentors, co-advisors and/or collaborators at multiple sites. The KL2 provides a career advisor in addition to the primary mentor, coupled with the explicit practice of having two advisors at different sites; this practice will be adopted for CTSTP trainees as well, particularly postdoctoral trainees.

Our CTSC has increased collaboration between investigators at participating institutions as supported by a "before and after" analysis of collaborative publications. Our CTSC was started in May 2007; given the lag to publication and for impact of CTSC innovations, publications in 2008 largely reflect pre-CTSC patterns of collaboration. The proportion of CTSC faculty who had at least one collaborative publication with another

CTSC faculty member in the reporting year rose from 58% in 2008 to 88% in 2012.[1] In addition, the proportion of faculty with inter-institutional collaborations (across our CTSC) rose from 25% in 2008 to 61% in 2012. In 2017, we plan to extend this analysis to include later years.

Research funding: Our robust mentor pool includes mentors with established training records and funding from NIH or other funding agencies (Table 4). The 65 mentors have a track record of research grant funding as PI and/or significant project leadership within a large team science program. The mean annual direct cost grant funding as PI per mentor is over $1,000,000 (bottom of Table 4).

Training record: The mentors have established training records with many prior trainees who have successfully established independent research programs. Table 2 demonstrates that most mentors have trained predoctoral and/or postdoctoral trainees who have successfully remained in research. The mentors are approved for specific stages of training (predoctoral, postdoctoral and KL2 trainees) as indicated in Table 2, depending on their training record and expertise. We also accommodate new mentors without an established training record ("Initial Mentors") who are on a very strong scientific trajectory, but trainees placed with Initial Mentors must have a senior co-mentor, and Initial Mentors must complete a mentor training program (section 3.2).

In addition to established senior faculty mentors, we encourage junior faculty to develop mentorship skills; this is facilitated by a mentor training program that is run with the KL2 program and a requirement for junior mentors to have a senior mentor as co-advisor for trainees (junior mentors are defined as those who have not yet established a substantial record as a mentor, e.g. having graduated a PhD student for predoctoral training or having productively mentored postdoctoral trainees to successful later stages of a research career).

The successful record of mentorship and training is demonstrated by the strong publication record of trainees of the participating faculty (Table 5). Table 5A illustrates the publication record of TL1-appointed predoctoral trainees of the participating trainers (per NIH instructions, trainees of past trainers are not shown in Table 5A, but they are shown in Table 8A, and we include them in comprehensive TL1 outcomes reported in the next paragraph). As we do not yet have a postdoctoral TL1 program, Table 5B reports the publications of general postdoctoral trainees (not specifically TL1-associated) of the training faculty.

Comprehensive analysis of all past TL1 trainees: Of the 17 MD-PhD students and 2 DNP-PhD students who have been supported by the TL1 and who have completed the program, all but one (a DNP-PhD student) have at least one first-authored publication from the training period, with a mean of 2.3 first-authored and 4.4 total publications from the training period, excluding abstracts. Thus, the trainers and program have a successful record of trainee publication, particularly for MD-PhD students (section 3.4.4 has a Plan for Improvement for the DNP-PhD program publication outcomes).

3.3. Proposed Training

3.3.1. Overview and objectives: The CTSTP is designed to train leaders in C/T research who will have a wide range of clinical and scientific skills to make important contributions to future C/T research. Trainees will come from all participating institutions of our CTSC (CWRU, CC, UHCMC, MHMC, VAMC) and will participate in degree programs based in the Schools of Medicine, Engineering and Nursing at CWRU. The program includes the following predoctoral and postdoctoral training pathways (Fig. 1).

1. Predoctoral MD-PhD training of physician-scientists in C/T research.
2. Predoctoral DNP-PhD training of nurse-scientists in C/T research.
3. Postdoctoral PhD in C/T Science for individuals with a prior clinical doctoral degree (or a relevant MS degree; the latter are actually predoctoral trainees but will follow the same curriculum as postdoctoral C/T Science trainees).
4. Postdoctoral C/T research fellowships for candidates with a strong research trajectory who need additional training to develop independence and compete for K08, K12, KL2 or other fellowship or research grants (including physicians, nurses, dentists, biomedical engineers or PhD C/T researchers).
5. Postdoctoral C/T research training in research-intensive residency/fellowship programs.

3.3.2. Approaches:

1. We will provide rigorous research training with a robust set of program activities, including coursework, mentoring, professional development activities and research forums and retreats.
2. We will motivate and inspire scholars to pursue careers in C/T science with role models, mentors, peers and programs that will inspire and nourish intellectual interests and instill a passion for research.
3. We will provide a training pipeline from the predoctoral phase through postdoctoral training that will prepare trainees to launch an independent research career and successfully compete for K grant and

other grant funding mechanisms.

4. We will support training in a wide range of C/T research fields and for a wide range of research career paths, including physicians, nurses, dentists, engineers, social scientists, and experts in informatics, health care delivery and other topics.
5. We will nurture a culture of **interdisciplinary, team-based research**.
6. Predoctoral and postdoctoral CTSTP trainees will participate in a core curriculum with team science training, professional development, RCR, IDPs and research training activities.

3.3.3. CTSTP Core curriculum. The CTSTP will include a diverse group of predoctoral and postdoctoral trainees in training programs in different scientific and clinical fields in medicine, nursing and dentistry. We will unify the program and insure critical core training in team science, C/T research issues and professional development aspects with core curricular components that will engage all CTSTP trainees from all participating programs. The core curriculum is described here; sections 3.3.5 and 3.3.6 describe predoctoral and postdoctoral curricula that will provide rigorous training in research methodology to promote best practices in C/T research and to minimize bias in experimental design and reporting.

Interdisciplinary and team science training: The CTSTP core curriculum will incorporate a curriculum in team science training that has been developed over the last 10 years through our KL2 and precursor K12 program. A team science thread includes formal coursework, seminars, and first-hand experience on research teams. The core feature is a formal for-credit course, CRSP 501, Team Science: Working in Interdisciplinary Research Teams, which is offered in the fall semester of each year (Dr. Moore, CTSTP Associate Director, is the course director.). This interdisciplinary course assists trainees to develop a set of skills specific to participating on and leading an interdisciplinary research team, including working with different value and knowledge sets across disciplines, understanding the mental models of other disciplines, creating shared mental models, running effective meetings, managing conflict, giving and receiving feedback, and group decision making techniques. Using the small group seminar approach and case studies, learners practice individual and group communication, reflective and self-assessment techniques, and engage in experiential learning activities regarding effective teamwork in interdisciplinary research teams. Techniques to increase group creativity and frame new insights are also discussed. This course has consistently received outstanding evaluations from the participants regarding its importance and usefulness to them. Last year, we included predoctoral trainees as participants in the course with good success. Thus, we now plan to include this course as part of the training for all our predoctoral and postdoctoral trainees. It is important to note that formal training in team science has also been made available to our mentors as well.

Multidisciplinary research seminars: Trainees will also participate continuously in a seminar course, CRSP 450, Seminar in Multidisciplinary C/T Research, offered fall and spring semesters. Leaders in C/T research present research advances and approaches to leading and managing C/T research, team science and other topics.

Shared retreats: The CTSTP will continue to share an annual retreat with the MSTP. All trainees who are in a research training phase do an oral or poster presentation. The retreat also features a prominent outside speaker, networking events and activities to expose trainees who have not yet chosen a research mentor to potential research mentors. CTSTP trainees will also participate in joint retreats with the KL2 program.

Individual Development Plans (IDPs): All trainees will complete IDPs. We have developed different IDP versions for combined degree predoctoral trainees and postdoctoral trainees that are tailored to the different professional development planning needs of these cohorts. The IDP is a web-based program that allows trainees to explore and develop professional development plans with input and review from their mentor. Trainees are guided through several sections that guide them in creation of their own long-term career goals (research, leadership, clinical, etc.), a series of questions to develop self-assessment and the setting of goals for professional development (e.g. competencies in grant writing, funding, leadership development, team science skills, networking, mentoring skills, seminar presentation skills; also plans for attending research conferences, professional development workshops). Trainees evaluate their interactions with their mentors and other advising faculty, and they identify any aspects of mentorship that they find lacking. Progress and plans for specific training activities are developed (courses, research rotations, RCR), including research progress, publications and grants. Plans are developed for completion of clinical training, if applicable, and integration of research with other future career goals. The mentor reviews the IDP with the trainee and provides both verbal and written feedback. IDPs are important for developing career goals and ensuring that conversations between the trainee and mentor about these goals occur on a regular basis. In the event that a trainee needs an additional mentor viewpoint, an additional IDP mentor can be designated for review of the IDP. The SOM encourages trainees to explore the myIDP web tool package that is available at

http://myidp.sciencecareers.org. IDP requirements: All student trainees complete an IDP within six months of their initial appointment, and postdoctoral trainees complete an IDP within three months of their initial appointment. Completing an IDP is an interactive process that involves face-to-face meetings and frank discussions between the trainee and mentor. The IDP is updated at least annually during the training period, including meetings between mentee and mentor. All IDPs and annual updates are submitted electronically to the CWRU SOM Graduate Education Office through the SOM IDP Portal (casemed.case.edu/idp). Compliance: Department Chairs and Program Directors are notified annually of trainee compliance. A SOM Graduate Education Office website tracks compliance in each department. The final submission process requires that both the trainee and mentor have viewed the document and have met to discuss its contents.

Activities to develop grant writing skills: The CTSTP core curriculum includes professional development activities shared with the KL2 program, including grantsmanship (postdoctoral trainees will particularly benefit from the KL2's online K Kiosk with resources such as guides and examples for K/R applications, career development plans, support letters and other grant-related issues). We hold F30/F31 grants workshops for MD-PhD students 3 times per year. In addition, grants workshops are sponsored several times each year by the School of Medicine office of Graduate Education. For predoctoral trainees, the thesis proposal in participating PhD programs is written in the format of an NIH grant proposal, and students receive critique to improve grant writing skills. A number of courses include writing of grant proposals (e.g. CRSP 412 Communication in Clinical Research – Grant writing).

Advising and Mentoring: Detailed advising and mentoring will support trainees at all stages, including involvement of primary scientific mentors, CTSTP advisors, and thesis committees (for predoctoral trainees) or mentoring committees (for postdoctoral trainees). CTSTP advising will be provided by the Director and members of the Steering Committee. The thesis or mentoring committee members will be chosen within six months (for predoctoral trainees) or three months (for postdoctoral trainees) of selection of the primary scientific mentor. The composition of the committee will be developed in discussion between the trainee, primary scientific mentor, and CTSTP advisors, and will be approved by the CTSTP Steering Committee (and the PhD program for predoctoral trainees). Predoctoral advising: Advising of MD-PhD students will be provided by the Director and members of the MD-PhD subcommittee (e.g. Drs. Spilsbury, Abbott, others). Advising for DNP-PhD trainees will be provided by Drs. Zauszniewski and Moore. Advisors from the PhD program and the clinical doctoral program (MD or DNP) will also provide important advising functions. Postdoctoral advising: For trainees in the C/T Science PhD program, the PhD mentor will be the primary advisor and Dr. Spilsbury will serve as program advisor (to provide programmatic and career advising and to check that progress and the mentoring relationship with the primary mentor is proceeding well). Postdoctoral trainees in C/T research fellowships or research track residencies/fellowships will have a primary scientific mentor who will be identified at the time of application to the CTSTP. In addition, Dr. Dweik or another Steering Committee member will serve as CTSTP advisor for trainees in C/T research fellowships, and Dr. Harding or another Steering Committee member will serve as CTSTP advisor for those in research-track residencies or fellowships; the directors of those research-intensive training programs will also provide advising.

3.3.4. CTSTP curricular options and national CTSC connections.

CTSC curriculum options: Beyond the TL1 core curriculum, TL1 predoctoral and postdoctoral trainees will electively take courses from the CRSP MS and C/T Science PhD program curricula. In the CTSC Community and Collaboration component, Dr. Sehgal has developed plans for a course "Integrating special populations in research," which will cover challenges in engaging and recruiting groups that are less likely to participate in research, e.g. racial and ethnic minorities, females, the poor, non-English speaking individuals, people with particular disabilities, rural dwellers, pregnant women, the LGBT community, and other "hard to reach" groups such as illicit drug users.

The Translational Workforce Development (TWD) Program (Aim 1 of Section D, CTSC application) will develop C/T research education programs to be used by the CTSTP and other education components of our CTSC, including workshops, webinars, podcasts and courses for C/T research training for both predoctoral and postdoctoral trainees. This program will create new innovative approaches and add expertise in the form of educational consultants and programmers/web developers, enabling the development of new electronic learning resources, such as webinars, podcasts and website content. Participation of the CTSTP will be fostered by the roles of Drs. Spilsbury and Moore, both Associate Directors of the CTSTP and both co-leads of the TWD Program. For example, Dr. Moore has developed team science training in the CTSTP core curriculum. Aim 1C of Section D of the CTSC application describes our development of web and mobile resources for TWD, providing a unified portal where scientists, students, staff can access training resources, identify

strengths and gaps in their knowledge by self-appraisal, and document progress towards individualized goals. A TransTrain app is being developed by the TWD Program; this app will allow self-appraisal, initiation of training engagements with CTSC programs, and navigation to a curated set of websites, podcasts, and videos.

National sharing and collaborations: These efforts will include sharing of content with CTSC partners. The web/mobile-app templates developed by the TWD Program will be shared with other CTSAs, and we will include content from CTSA partners, e.g. Harvard CATALYST (supporting letter provided for section D of the CTSC application). These approaches will allow trainees to get exposure to team science concepts that have been vetted and benchmarked nationally.

The Clinical Research Team Training Taskforce is an ongoing CTSC initiative headed by Dr. Spilsbury that develops Good Clinical Practice and Responsible Conduct of Research (RCR) guidelines across all of our CTSC institutions. Although each institution has individual responsibility for compliance, the Taskforce harmonizes training elements across the CTSC and includes important partners (e.g. Case Comprehensive Cancer Center, Center for AIDS Research and other major clinical centers) in meetings to serve their needs and interests. The Taskforce received an NCATS supplement award (3UL1TR000433-0851, 2014-2015) to streamline and standardize training in Good Clinical Practice across the entire CTSA consortium.

The TL1 will work with the TWD Program to incorporate the NSF I-Corps training program into a skills development program to foster entrepreneurship. This program will address major impediments to translation of research from the bench to the bedside, including the lack of understanding of requirements and approaches for commercialization. The CC has piloted an NSF I-Corps Hub (led by CTSC TWD Program Co-lead Dr. Reizes) in collaboration with the recently established NIH Center for Accelerated Innovations to enhance the education and mentoring of researchers, clinicians and developers, and to advance the commercialization of technologies from their respective funded research programs. This pilot will provide a foundation for incorporation and broader application of the I-Corps training program within the CTSC. Example applications include training in the Lean Launchpad Business Model. As this program develops, we will share curriculum and best training practices with other CTSC Hubs within Ohio and nationally.

National outreach: Sharing best practices with other CTSAs is a high priority for our CTSC. The CTSC is part of the Ohio Consortium of CTSAs, which includes Ohio State University's CCTS and University of Cincinnati's CCTST (in July, 2013 the CTSTP and MSTP held a joint retreat with Ohio State). This consortium was funded by NHLBI in 2012 as part of the National Centers for Accelerated Innovations program, composed of the Ohio consortium and two other consortia, the Boston Biomedical Innovation Center and the University of California Biomedical Research Acceleration, Integration and Development Center. Our membership in the consortium has led to our partnership with the Harvard CATALYST program, allowing us to share ideas about best practices across CTSAs and brainstorm new pilot initiatives. (See Section D, CTSC application)

3.3.5. Predoctoral MD-PhD training of physician-scientists in C/T research. The curriculum for training MD-PhD students in the CTSTP (Fig. 2, Table D) involves integration of research and clinical training, a focus on C/T research, professional development and team science training.

CTSTP MD-PhD Training Program

Year in program	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
First 2 years MD program								
Graduate rotations & courses								
PhD Research*, complete coursework								
Integrated clinical tutorial (1-2 years)								
Clinical clerkships, clinical & research electives								

*PhD Research lasts 3-5 years, averaging ≈4 years.

CTSTP DNP-PhD Training Program

Year in program	Year 1	Year 2	Year 3	Year 4	Year 5
DNP and PhD courses					
Research practicum					
Leadership electives					
Integrated clinical practicum					
Proposal development & candidacy exam					
Scholarly DNP project					
Dissertation					

Fig. 2: CTSTP Predoctoral Timelines: CTSTP students complete an MD or DNP and a PhD in a C/T research field in an integrated curriculum.

Table D. CTSTP MD-PhD curriculum outline[1]	
Year (M=Med; P=PhD)	Curriculum Components
M1	MD curriculum July-May (Grad credits as IBIS 401, 402, 411, 412) Research rotation in afternoon during incoming summer Graduate course[2] (3–4 credits) or research rotation in fall and spring
Summer (10 weeks)	Research rotations (two, five-week rotations or one long rotation)
M2	MD curriculum August–February (Grad credits as IBIS 403, 413) Research rotation or grad course (3–4 credits) in fall (finalize PhD lab choice) Graduate course[2] in spring semester (3–4 credits) Review and completion of USMLE part I by April PhD research starts by end of April
P1	Research, advanced graduate courses[2] Qualifying examination and thesis proposal near end of P1
P2	Research and publication Required: MD-PhD Clinical Tutorial
P3-4	Research and publication, defend thesis Recommended: second year of MD-PhD Clinical Tutorial
M3	Flexible timing to start M3 July–November Core clerkships and electives; segments for research in some sequences.
M4	Clinical and research electives
1. Continuous: Research seminars, CTSTP professional development activities, IDPs, RCR (IBMS 500 and RCR+4). 2. Includes CRSP 501, Team Science: Working in Interdisciplinary Research Teams.	

In the first two years of medical school (M1–M2), graduate school courses and research rotations are integrated into all semesters; MD-PhD students complete 3–4 research rotations and ~3 graduate courses (3–4 credits each) by the end of M2. This integrates research training into M1–M2, facilitates exploration and progress of the graduate program in this period, and accelerates progress when the PhD phase is reached.

In the PhD phase, students perform rigorous, original research, publish first-authored papers in peer-reviewed scientific journals and satisfy all PhD program requirements. A minimum of one first-authored, peer-reviewed paper is required prior to the PhD defense, and most participating PhD programs require two first-authored papers. Integration of clinical training with the PhD phase: In the PhD phase, CTSTP students must take at least one year of the MSTP/CTSTP Clinical Tutorial (a second year is strongly encouraged). This program involves individualized placement of students into specific clinical fields of interest. Students spend one half day per week throughout the academic year working in a clinical setting with a clinical mentor in a field of their choice. Mentors with clinical or translational research programs are preferred as role models who will further emphasize connections between research and clinical experience. This allows students to explore connections between their research interests and an individually chosen clinical setting, facilitating impact on career development and choice of field. The longitudinal aspect of this program allows greater integration of research and clinical interests, much like the careers of physician-scientists beyond training.

M3–M4: Students complete remaining clinical training requirements for the MD and take research electives to extend their PhD research or explore new areas.

TTD: Separately, the MD degree takes 4 years and a PhD a mean of 5.5 years. CWRU MD-PhD students complete both degrees with a mean time to degree of 8.3 years (8.4 years for the 17 MD-PhD graduates who were supported on the TL1) in a curriculum that integrates graduate school coursework into the first 2 years of medical school, and clinical training into the PhD phase.

PhD programs for CTSTP MD-PhD students:

C/T Science PhD program: Launched in 2015, this PhD program accommodates two training pathways: PhD training for individuals with a prior clinical doctoral degree or a relevant MS degree (section 3.3.7) and predoctoral combined degree MD-PhD training (this section). The program provides trainees with professional and research skills to become productive researchers in C/T science. The curriculum totals 69 credit hours and is based on nationally developed core competencies for this field. The 18 credit-hour, required core curriculum covers four key domains: 1) clinical and translational theory, practice, and perspectives ("Translational and Patient-Oriented Theory," "Seminar in Multidisciplinary Clinical & Translational Research"); 2) research methods ("Meta-analysis and Evidence Synthesis," "Study Design and Epidemiologic Methods"); 3) statistical science (core topics including linear and logistic regression, survival analysis, power analyses, modeling); 4) professional development ("Team Science-Working in Interdisciplinary Research Teams," "Leadership Skills for Clinical Research Teams," "Grant Writing," "Oral Presentations, Posters, and the Mass Media"). Elective

coursework is selected based on individuals' field-specific and statistical/methodological needs: e.g., immunology, neurology, cancer, structural equation modeling, qualitative/mixed method approaches, clinical informatics, data management, clinical trial design, comparative & cost effectiveness analysis. Trainees are immersed in research activities through research rotations and then PhD dissertation research.

The program's interdisciplinary 42 core faculty members involve all CTSC institutions and numerous departments and centers, including the Case Comprehensive Cancer Center; the Centers for Clinical Investigation, Proteomics & Computational Science; the Departments of Epidemiology & Biostatistics, Pharmacology, Genetics, Family Medicine and Community Health, Molecular Biology and Micro-Biology; the Frances Payne Bolton School of Nursing; the School of Dental Medicine; the School of Engineering; and clinical departments at all CTSC affiliates. Program faculty are involved in a wide range of clinical and translational research domains: e.g. genetic/molecular epidemiology of cancer, cystic fibrosis, kidney disease, diabetes, and other complex diseases; pharmacogenetics; infectious diseases and antimicrobial resistance; innate immunity; medical decision making; cardiac rehabilitation; behavioral interventions; medical anthropology; oral health in special-needs populations; health disparities. Dr. Li Li is the Director; he is on our CTSC TWD Advisory Board. Dr. James Spilsbury is the Co-Director; he is also CTSTP Associate Director and a CTSTP Steering Committee member.

Mentoring is critical to students' success in the program and to their overall career development. Each student has a primary mentor to provide guidance for the student's PhD research and training. In addition, each student has a co-mentor to provide complementary guidance related to the student's overall program of study, career plans and overall professional development. Both mentors are selected based on the students' research interests, and have established track records of mentoring and funded research.

In the two years since its launch in 2015, the C/T Science PhD program has had 2 MD-PhD entrants and 5 entrants with a prior clinical doctoral degree or relevant MS degree (section 3.3.7 addresses postdoctoral and prior-MS degree trainees).

Epidemiology and Biostatistics: Trainees complete a rigorous integrated core of coursework in both epidemiology and biostatistics, including courses in epidemiology; biostatistics; health services research; integrated and quantitative methods in population health sciences; ethical, legal and social issues in population health; and scientific reading and writing. Areas of concentration include Genetic Epidemiology and Bioinformatics; Global Health Epidemiology; Health Behavior and Prevention; Modern Biostatistics; and Health Care Organization, Outcomes and Policy. Specific coursework includes genetic epidemiology, statistical analysis in genetic epidemiology, population genetics, bioinformatics, global health, infectious disease epidemiology, health disparities, management of disasters, health behavior, evidence-based prevention strategies, pathophysiological consequences of behavior, measurement of health and health behavior, comparative and cost effectiveness research, and analysis of large healthcare databases.

Faculty research topics include the areas listed above along with statistical genetics applied to family and pedigree data relating to complex genetic traits, especially chronic diseases; systems biology and bioinformatics; infectious diseases; behaviors and environments related to chronic disease prevention and health promotion; analysis of electronic medical records and "big data"; clinical informatics; development, implementation, and evaluation of community interventions; immunizations and screenings. There are 36 primary faculty. Primary faculty with leadership roles in the CTSTP include the Chair, Dr. Jonathan Haines (TWD Advisory Board) and Dr. Cathy Stein (CTSTP Steering Committee).

Biomedical Engineering (BME): The BME PhD program has strong translational research and training components. In collaboration with all four hospital affiliates, translational topics with direct clinical application are approached with novel engineering technologies. Students take coursework (e.g. systems engineering and instrumentation) that is integrated with relevant clinical training and training in clinical research (e.g. clinical pharmacological dynamics, statistics, epidemiology). The core curriculum includes four required engineering courses including bio-instrumentation, signal processing, cellular and molecular biology, physiology and modeling. Electives include mathematical and biomedical courses. Activities include clinical conferences relevant to the research area, an optional summer internship with a biomedical device company, research rotations in clinical departments, courses with strong clinical relevance (rehabilitation engineering, cardiac bioelectricity, clinical research seminars, clinical research methods, training in regulatory affairs and human subjects research, training in communications with medical professionals). Research training areas include biomaterials and implantable prosthetics, orthopedic implants, neuroprosthetic devices, neuromodulation functional electrical stimulation, BioMEMS, nanoengineering, medical instrumentation, microscale sensors, biomedical imaging, interventional MRI, orthopedics/biomechanics, drug delivery rehabilitation engineering, big

data analytics, health informatics, metabolomics, system biology, and tissue engineering. Research training integrates quantitative engineering, clinical research, participation of human subjects and development of enabling technologies for clinical diagnosis and treatment. Faculty: There are 29 primary and 60 secondary BME faculty. BME programs and faculty are present at CWRU, CC, UHCMC, VAMC and MHMC. Active participation in both SOM and SOE, and all affiliated hospitals, provides a collaborative environment to establish many research centers and translate biomedical engineering research from bench to bedside. The Chair of BME, Dr. Robert Kirsch, serves on the TWD Advisory Board. BME faculty on the CTSTP Steering Committee include Drs. Eben Alsberg, Dominique Durand and Nicole Steinmetz.

Systems Biology and Bioinformatics: A new interdepartmental PhD program in Systems Biology and Bioinformatics (SYBB) was launched in 2011, since then it has grown to its current cohort of nine PhD students (plus 10 students in its accompanying MS program). The SYBB program embraces a holistic experimental and quantitative approach to answering complex biological questions, relating how higher level properties of complex biological systems arise from the interactions amongst their parts. The SYBB program is administratively housed in the Center for Proteomics and Bioinformatics, Department of Nutrition, and brings together more than 30 highly qualified faculty distributed among diverse departments ranging from computer science, epidemiology and biostatistics, math, nutrition, proteomics, pharmacology and biophysics. The research topics studied by SYBB trainers include HIV latency, structural biology, proteomics methods, designing targeted therapeutics for cancer, understanding cell signaling, and developing algorithms/software for the analysis of genomic, proteomic metabolomic data. This integrative program is individually tailored to each student's research topic; students matriculating through the SYBB program have only two required core classes, SYBB 411 and 555, which introduce 'omic approaches and techniques. SYBB students in close consultation with faculty mentors design a tailored program of study that ensures competency in both computational and experimental approaches to answering questions arising from "big data." The program currently offers two research tracks for specialization: 1) A Translational Informatics Track which places students at the interface between 'omic approaches to research and clinical medicine; and 2) A Molecular and Computational Biology track which develops and applies computational models/approaches to understand complex biological systems. The Director of the SYBB program, Dr. Mark Chance, serves as Chair of the TWD Advisory Board.

Other PhD programs: In addition to the four PhD programs identified above, CTSTP MD-PhD students may train in other PhD programs on topics that are of C/T focus (Table A).

3.3.6. Predoctoral DNP-PhD training of nurse-scientists in C/T research.

The Nursing PhD program includes 57 credits: 36 credits for coursework, three credits for proposal development, and 18 credits for the dissertation. Core courses include knowledge development and theory (six credits), research methods (nine credits), statistics (nine credits), and specialized courses related to the individual student's research interests (12 credits). Coursework in research training includes two quantitative and one qualitative research methods courses. Statistics courses include a graduate-level basic statistics course and courses in linear models and multivariate techniques. A research practicum provides hands-on experience in the conduct of research under faculty mentorship. After completing the required courses and research practicum, students must pass an oral candidacy exam and defend a written research proposal. Following advancement to candidacy and successful proposal defense, students complete their research and final dissertation.

Nursing PhD students and mentors: The nursing PhD program currently has 50 students, including 5 BSN to PhD students, 44 MSN to PhD students, and 3 DNP-PhD students. There are 29 faculty in the SON who are approved as PhD mentors. We have increased the rigor of CTSTP mentor approval, and only the subset of Nursing PhD trainers who have been approved as CTSTP mentors will be allowed to take DNP-PhD students.

Dual Degree (DNP/PhD) Curriculum: Students in the DNP-PhD program complete courses in a "side-by-side" fashion with courses in both doctoral programs taken concurrently, with an allowable overlap of 11 credits. Overlapping courses are in health policy, research methods, basic statistics, and proposal development. The dual doctorate includes 78 credits: 55 credits for coursework, three credits for proposal development, two credits for the DNP scholarly project, and 18 credits for the PhD dissertation. The program can be completed in four to five years.

3.3.7. PhD program in C/T Science – curriculum for postdoctoral or prior-MS trainees.

For individuals already holding a clinical doctoral (or in some cases a relevant MS degree) the 54 credit-hour curriculum covers the 4 key domains and elective areas described in section 3.3.5. In addition to the 2 MD-

PhD entrants mentioned above, 5 students have matriculated into the program in the two years since its launch in 2015: three with a prior MD and two with a prior MS degree (the latter are predoctoral trainees but follow a C/T science training sequence similar to the "postdoctoral" pathway, not the integrated MD-PhD training sequence described in section 3.3.5). The research interests of these trainees include: the interplay of genetics and gender to develop personalized care for persons with severe asthma; use of simulation modeling to optimize colon-cancer screening strategies; genetics of human-H. pylori interactions that lead to gastric cancer; improving care of persons with kidney disease by changing practices of dieticians and nutritionists at dialysis centers; use of traditional epidemiological and systems-biology approaches to better understand why and how cancers metastasize to the brain; novel use of statins to treat hair loss in cancer; and translating discoveries in the laboratory into improved blood transfusion and organ transplant procedures.

3.3.8. C/T research fellowships will be supported for candidates who are on a strong research training trajectory but need an additional period of research training to be competitive to apply for a K08, K12, KL2 or other award. These trainees may include physicians, nurses, dentists, biomedical engineers or other PhDs who aspire to C/T research careers. They will engage in a minimum period of research of two years of mentored research and will participate in the CTSTP core curriculum in team science and professional development activities (see section 3.3.3). Coursework may be taken in the CRSP (below) or other programs.

3.3.9. Postdoctoral C/T research training in research-intensive residency/fellowship programs. Research track residents/fellows will be recruited through the programs listed in Table B. After arrival, they will receive advising from their research track residency/fellowship program, they will be connected to the CTSTP and its curriculum, and they will be invited to apply for TL1 support (identification of a mentor and research project will be a prerequisite). They will engage in a minimum period of research of two years of mentored research and will participate in the CTSTP core curriculum in team science and professional development activities (Fig. 1 and section 3.3.3). Coursework may be taken in the CRSP or other programs.

3.3.10: The Clinical Research Scholars Program (CRSP) leads to an MS in Clinical Research and is open to both post-doctoral and pre-doctoral trainees. Within the CTSTP, the CRSP will be most applicable to trainees in the C/T research fellowships or research-intensive residency/fellowships. The CRSP curriculum overlaps with that of the PhD in C/T Science and includes the CRSP 501 Team Science course that is part of the CTSTP core curriculum. The CRSP prepares graduates to identify a research question, critically evaluate the relevant scientific literature, transform the question into a feasible study design, develop and execute a study protocol, and analyze and effectively communicate the findings. CTSTP trainees may complete an MS in the CRSP or take some of the coursework of this program without completing an MS degree.

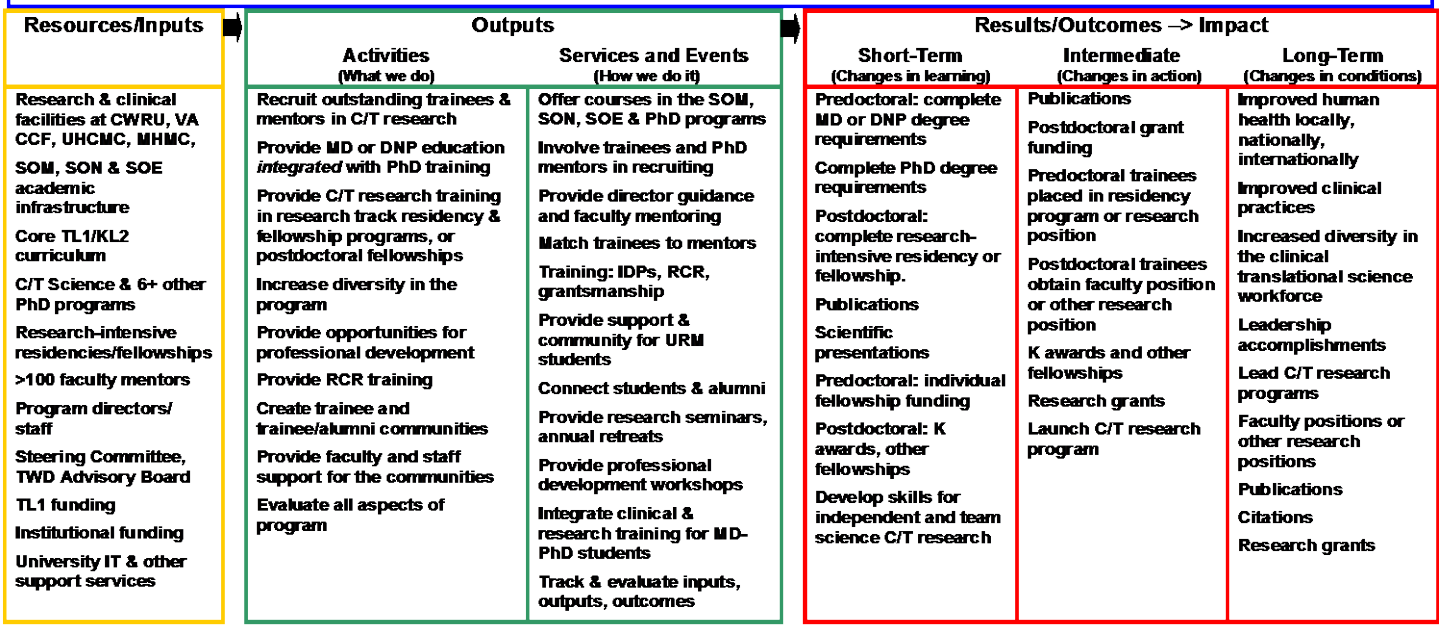
3.3.11. Trainee participation in research: Trainees are expected to engage deeply in rigorous research. The research training period for postdoctoral trainees will be a minimum of two years (with ≤25% clinical effort). For predoctoral trainees and postdoctoral trainees without extensive prior research background, the research training period will be longer. Trainees are expected to take leadership of their projects with appropriate mentorship; rigorous scientific publications and development of grant applications are also expectations.

3.4. Training Program Evaluation

3.4.1. Overview: Evaluation is a high priority in the CTSTP because we use it to drive continuous improvement and to engage trainees and mentors with our goals and expectations. Evaluation involves collaboration of the CTSTP Director, CTSTP Administrative Director (Kathryn Schultz, MS, MBA), the CTSC Evaluation Director (Clara Pelfrey, PhD) and the Steering Committee. Evaluation is ongoing and continuous. Regular progress reports include the TL1 annual progress report and a CTSTP Annual Report (shared with the entire CTSTP community, including trainees, mentors and relevant academic leaders at all participating institutions). Continuous evaluation will include discussion of progress and problems for trainees, mentors and program activities at the monthly Steering Committee meetings with documentation of outcomes and plans. Table E summarizes evaluation domains and metrics; Fig. 3 shows the CTSTP Logic Model with the outputs and outcomes that we will assess. Dr. Pelfrey serves on the NCATS Common Metrics workgroup; thus, we are prepared to update NCATS Common Metrics for Workforce Development as they develop. The footnote to Fig. 3 lists common metrics (proposed and/or implemented), and we have mapped them to our own metrics and data sources using the superscripted letters.

Sources of data: Evaluation will be supported by the extensive CTSTP database (institutional records of application and admissions, trainee progression, trainee publications, grant support, mentor review, program activities, alumni records) complemented by the KL2 and Graduate Education databases as well as data from the participating MD, DNP, PhD and research track residency/fellowship programs. We monitor positions that

Figure 3. Logic Model and Metrics for the CTSTP. Goal: Train future leaders in C/T research.



Selected *Key* Metrics (things to count or measure to evaluate the effectiveness of the program)

Resources/Inputs	Outputs	Results/Outcomes/Impact: Short-term	Intermediate	Long-term
[1,4,6,7,8]Mentor publication, training, and funding record Participating departments and PhD programs Participating institutions Program budget Team Science Training [E] Diversity Plan [A]	[3]Applications to program [1,2]Students recruited to program [1,2]URM applicants and entering students [4,5]Courses completed [5]Course grades [4]Seminars and workshops attended [2]IDPs completed [7]RCR training completed [4]Residency placements	[1,5]Students completing degrees [1,5]URM students completing degrees [F,G] [4]Diversity climate survey [1,2,5]Time to degree [4,6]Publications [D] [4]Research presentations [4]Pre-doctoral grants or fellowships	[4]Residency or research position placements [B] [1,4]Diversity of residency or research position placements [B] [1]Residency programs [4,6]Publications [D] [4,7]Post-doctoral grants and fellowships [B]	[4,9]Faculty or other research positions [B] [4,7]Grants [E] [4,6]Publications and citations [D] [4]Leadership accomplishments Improved clinical practices Increased diversity of the research workforce

Data Sources: [1]Program database, [2]SOM Graduate Education databases, [3]AMCAS application data, [4]Student, mentor & alumni surveys (e.g diversity survey), [5]University Registrar, [6]PubMed, [7]NIH Reporter, [8]University Grants and Contracts database, [9]LinkedIn, Internet searches.

NCATS Common Metrics (*proposed*) for Workforce Development
[A]New educational innovations, [B]Sustainable careers in CTR, [C]Percentage of grants, [D]Trainee publications, [E]Team science training, [F]Representation of URM/women,
[G]Innovative processes targeted to URM

trainees obtain upon completion of the program. We survey alumni to obtain feedback on the program, identify areas for improvement and determine alumni career activities and training outcomes. We also monitor alumni outcomes by database searches (e.g. LinkedIn and Google for professional positions, for alumni publications via PubMed, alumni grants via NIH Reporter).

3.4.2. Trainee evaluation of program and mentors: We will survey all trainees for individual evaluation of program and mentors. We will solicit feedback from MSTP/CTSTP Student Council and postdoctoral trainee groups. We will design trainee evaluation of mentors with consideration of other studies.(1) and established tools (e.g. https://mentoringresources.ictr.wisc.edu/EvalTemplates).

Mentors will also be assessed by the CTSTP Steering Committee as described in section 3.2.

3.4.3. Ongoing evaluation of trainees: Trainees are evaluated by their mentoring committee and the Steering Committee on a regular basis (at least twice per year). Trainees experiencing difficulty are discussed by the Steering Committee on a monthly basis. Each mentoring committee contains a member of the CTSTP Steering Committee to facilitate communication and evaluation. Mentoring committee reports will be reviewed by the Steering Committee. MD-PhD students must pass USMLE board part 1 at

Table E. Evaluation domains and metrics.

Trainee progression and completion of program requirements: publications, scientific presentations, grants, awards/honors, leadership accomplishments, curricular progression (courses, qualifying exam/thesis proposal, PhD dissertation), TTD.

Trainee recruiting and qualifications of applicants and matriculants: Competitiveness, diversity (URM, gender, disabilities, scientific fields), size and institutional sources of applicant pool, recruiting approaches (involvement of trainees and mentors).

Development and utilization of CTSTP curriculum: Team science, RCR, IDPs, K Club professional development, retreats, seminars, grants workshops.

Alumni outcomes: positions attained, research activities, grants, leadership accomplishments.

Mentors: number, quality and diversity of mentors, participation in mentor development activities, collaborative connections, publication and grant productivity, trainee evaluation of mentors.

Program: effectiveness of program design, curriculum and events: assessed by Steering Committee and trainee Council (section 3.1).

Program leadership: assessed by Advisory Board, trainees.

the end of M2 (100% of students have passed). Postdoctoral trainees will be expected to pass relevant board examinations for their clinical specialties. Trainees are evaluated for attainment of publications, grants, curricular progression and other targets indicated in Table E & Fig. 3.

If trainees experience difficulties, the Director and Steering Committee will work with the trainee to assess issues and factors and develop an advising plan, a remediation plan, or other support mechanisms to promote trainee success. As needed, trainees may be referred to educational services, counseling services, student affairs or other institutional advisors for coordinated support. The Director may engage mentors and thesis/mentoring committee members, including the Steering Committee representative to the thesis/mentoring committee. The trainee may be required to attend a Steering Committee meeting and present a progress report. If necessary, the Steering Committee makes disciplinary decisions for trainees and mentors.

3.4.4. Ongoing program evaluation: Program statistics are monitored annually, including time to degree, number of publications, honors, grant awards, position obtained after training and other targets.

Recruiting & admissions processes are reviewed and outcomes are analyzed in detail each June (to assess outcomes of an admissions cycle) and September (to consider best practices and potential changes for the upcoming cycle). See section 3.5.

Appointments to the TL1: There are 11 TL1 slots, and all of them have been filled every year with three remaining appointments that we will make in this budget period (Table 7).

Predoctoral trainee progression (Table 8A): Our TL1 grant has supported a total of 59 student trainees, including 54 MD-PhD students and 5 DNP-PhD students. Nineteen have graduated (17 MD-PhD students and 2 DNP-PhD students). These students had a mean of 2.3 first-authored papers and 4.4 total scientific publications, indicating consistent strong productivity of these students. Most trainees are still in the program (36 current students, including 3 DNP-PhD students and 33 MD-PhD students). Of 12 MD-PhD students who started in 2009 or earlier, three (25%) have been awarded F30 fellowships, indicating competitive success of our trainees. Four students have dropped from the program (discussed below). Not included in the preceding CTSTP numbers are 9 MD-PhD students (Table 8A, part II) who entered in 2016 and have not yet committed to a PhD program or received support from the TL1 but have expressed intent to enter a CTSTP research training area.

TTD: The mean time to completion of both degrees in combined degree training (MD-PhD or DNP-PhD) is 7.9 years (Table 8A, part IV; 8.4 years for the 17 MD-PhD graduates and 4 years for the two DNP-PhD graduates).

Publication productivity by trainees is monitored in a continuous fashion during the training period. Of the 17 MD-PhD students who have completed the program, all have at least one first-authored publication, with a mean of 2.5 first-authored publications and 4.9 total publications, excluding abstracts. This level of publication productivity provides a solid foundation for the future careers of CTSTP students as productive scientists. Note: These data are comprehensive for ALL past MD-PhD TL1-appointed trainees. Per NIH instructions, Table 5A lists only TL1-appointed trainees of participating trainers; trainees of past trainers are not included in Table 5A. Of the two DNP-PhD graduates, Swickard had one first-authored publication, but Balthazar did not have a publication. Nonetheless, this means that only one of the 19 total TL1 graduates was without a first-authored publication, and TL1 trainees (MD-PhD and DNP-PhD combined) completed the program with 2.3 first-authored and 4.4 total publications.

PLAN FOR IMPROVEMENT for DNP-PhD publications: Dr. Harding (TL1 Director) and Dr. Zauszniewski (DNP-PhD program director) have developed a plan and expectation for DNP-PhD trainees to have at least one first-authored publication. To achieve this goal, we will be implementing more rigorous admissions criteria for DNP-PhD students (e.g. to require a greater degree of prior research experience), revised approaches to mentor selection (trainers with poor trainee publication records have been removed from the mentor pool), project selection, student mentoring and Steering Committee oversight to enable this expectation. In summary, all of the MD-PhD trainees and 18 of the 19 total trainees who have graduated from the program have first-authored publications, and we are vigorously addressing the publication outcomes for the DNP-PhD program.

After graduation: Of 17 CTSTP MD-PhD graduates, 15 entered residencies immediately after completion of the program, one joined a biotechnology company and has become a leader there (Global Clinical Research Strategist) with 7 patents granted 2015-2017, and one obtained a faculty position immediately after graduation and now works as a data scientist at a medical informatics/technology company with a continued academic appointment. Those who entered residencies/fellowships were accepted in strong academic programs, including programs at Johns Hopkins, Stanford, Boston Children's, NYU, University of Washington, CC, UHCMC, Brigham & Women's/Harvard, Emory, U Chicago. While the program is young enough that only 3

MD-PhD graduates have completed residency/fellowship training, 6 past trainees have already received some grant support (Table 8A). The DNP-PhD program has only been in existence since 2011, so there is only a limited period in which to assess outcomes. We have had 5 DNP-PhD trainees, all of whom have been supported on the TL1 grant. Three are still in training, and two (Swickard and Balthazar) have graduated (one is Director of Clinical Operations, Mercy Health Life Flight Network, an area related to his research; the other is a nurse practitioner at a clinic that serves an underserved Native American population, related to her research interests).

Drops from the program: Four of the 59 trainees supported by the TL1 have dropped from the program (6.8%). While we are concerned to reduce our drop rate, we note that the trainees have accomplished significant goals. Three of these have completed their MD degree and are in residency programs; at least two of these still aspire to academic careers with research. The other prior CTSTP MD-PhD trainee who dropped, Rick Arlow, is already having significant impact in C/T research. During his CTSTP training, he developed a new device for human airway intubation that resulted in patented product development. He is also the co-founder of a start-up company (LifeServe Innovations), and he gave a prominent oral presentation at the 2010 National Predoctoral Clinical Research Training Program Meeting. In addition, he is a founding member of the Case Entrepreneurs Club and a finalist for Bloomberg BusinessWeek's "America's Best Young Entrepreneurs Award." He left the PhD program to devote himself full time to his start-up company LifeServe Innovations in developing software to support clinical research applications, including FDA regulatory issues. This is a positive outcome despite the fact that the program was not completed. PLAN FOR IMPROVEMENT: When a student drops before completion of the PhD, one possible explanation is that their preparation for research may have been inadequate. To enhance success in the PhD phase, we intend to increase focus during admissions selection on the extent of research experience (as evidenced by documented research experience, letters of recommendation, student essays and student interview performance with in-depth scientific discussion). We also plan to enhance advising and mentoring by faculty and students to promote success in engaging with a mentor and PhD program. For MD-PhD trainees, we are implementing a new course "Introduction to MD-PhD training", which will occur in their incoming summer semester, to enhance their scientific background (data interpretation, experimental design, critique of papers and grants) and mentoring for selection of a research mentor and PhD project.

Postdoctoral trainee progression (Table 8C): Our TL1 proposes future postdoctoral training but has not yet supported postdoctoral trainees to report in Table 8C, part I or part II. Table 8C part III shows 20 recent graduates of programs from which TL1 trainees will be recruited, of whom 65% have achieved research-related positions, 25% are in research-related positions, and 10% are in clinical practice without research; 50% have achieved some research funding (not including department start-up funds). These data reveal a strong record of developing research careers. Since these programs have been launched or expanded recently and have yet to participate in the TL1, the track record is not yet extensive. It is important to note that these trainees are NOT CTSTP TL1 trainees, but represent participating programs from which we will draw applicants – THE TL1 WILL SELECT THE MOST COMPETITIVE SUBSET OF TRAINEES FROM THIS POOL.

3.5. Trainee Recruitment and Candidates

Competitive candidates with commitment to research will be recruited nationally to enter medical or nursing school as dual-degree CTSTP students, or for postdoctoral research training. Trainees will be selected based on commitment to & promise for productive careers in C/T research. Criteria include prior academic performance, standardized test scores, recommendation letters from research advisors & interview evaluations.

Three subcommittees of the Steering Committee will each manage one applicant type: predoctoral MD-PhD applicants, predoctoral DNP-PhD applicants or postdoctoral applicants (the latter will also review predoctoral candidates with prior MS degrees for the PhD in C/T Science). The full Steering Committee will review and oversee the actions of the subcommittees, particularly with regard to recruiting efforts, admissions procedures, and the impact of admissions decisions on the balance of training in different areas supported by the CTSTP. For example, biomedical engineering (BME) will remain an important area of training in the CTSTP, but our plans involve a reduction in the proportion of CTSTP predoctoral trainees in BME as we ramp up training in our newer PhD programs in C/T Science and Systems Biology & Bioinformatics.

3.5.1. Predoctoral MD-PhD recruitment of applicants for MD-PhD training in C/T research. National recruitment is developed by Steering Committee members and current students who visit undergraduate institutions, pre-med fairs and national meetings. We make special efforts for recruiting of URM trainees (section 4).

Application and admissions procedures: The CTSTP and MSTP share an online MD-PhD admissions program

that is executed in conjunction with the MD admissions process. AMCAS MD-PhD applicants complete the AMCAS primary application and an on-line CWRU SOM secondary application, "iApply", which includes identification of fields of research interest for MD-PhD training (a pull down menu includes all of the CTSTP-affiliated PhD programs). Application data flow from the CWRU AMCAS portal and iApply to the CTSTP, MSTP, CCLCM and University MD programs. Members of the Executive Committee and the MD-PhD subcommittee review applications to select interviewees, who visit for a two-day intensive visit that includes interviews by three Steering Committee members, approximately three other CTSTP mentors, and representatives of the MD program. Interview comments are submitted through an electronic portal and merged with application data for review, and admissions decisions are made by the MD-PhD subcommittee of the Steering Committee on a rolling basis from October through April. The full Steering Committee monitors and approves decisions by the subcommittee to manage the balance of admissions in different areas covered by the CTSTP.

Criteria for selection and appointment: Selection of candidates is based on academic accomplishment (grades and selection of rigorous science courses, GPA, MCAT) with a heavy emphasis on evidence of research skills and commitment to research (recommendations by research mentors, posters and publications, research essay, in-depth scientific discussions during interviews). Interviews are crucial for assessing scientific sophistication, drive and motivation, accomplishment, state of development of career goals, presentation skills, verbal skills, interpersonal skills, etc.

Applicant tracking: A database includes data imported from AMCAS, including numerical data on applicants, which is reported to the Steering Committee for monthly evaluation during recruiting season. The Steering Committee reviews the recruiting track record in June and reviews admissions procedures in September to adjust procedures when necessary to promote success in recruiting qualified students.

3.5.2. Predoctoral DNP-PhD recruitment: Students will be recruited nationally by outreach efforts of the faculty in Nursing. This program represents one of only roughly four DNP-PhD programs in the U.S. Applications will be evaluated by the DNP-PhD subcommittee of the Steering Committee. Applicants will have interviews with three members of the DNP-PhD subcommittee and additional CTSTP mentors from the Nursing PhD program, as well as DNP program representatives. DNP-PhD admissions will be made by the DNP-PhD subcommittee with review and oversight by the full Steering Committee. The criteria for admission will include evidence of strong academic performance in earlier stages of training in nursing and commitment to pursue research.

3.5.3. Postdoctoral recruitment: Different approaches will be used for recruitment of each of the three postdoctoral applicant streams. These approaches will be managed by the Postdoctoral subcommittee with oversight by the full Steering Committee.

A. C/T Science PhD program recruitment will involve: 1) advertisements in selected electronic and printed journals and publications; 2) publicizing the program and contacting potential students at relevant scientific conferences and meetings (e.g., the annual Translational Science meeting; we will also target meetings with diversity recruitment opportunities, e.g. the ABRCMS meeting, see section 4); 3) communications to CTSC partner institutions. Admissions decisions are based upon rigorous assessment by the Steering Committee of an applicant's academic record, letters of reference, research essay, and interviews. The applicant's training in mathematics and statistics is also assessed, assuring that candidates for admission have suitable background for the program's statistical science courses. The program tracks the number of applications it receives each year, including the educational/training background of each applicant.
B. C/T research fellowships will be provided for postdoctoral trainees who are too early in development for a K award but are on a strong trajectory and will likely benefit from one to two years of C/T research training with TL1 support before being ready to apply for K, R or fellowship grant support. We will expand the extensive recruitment and application process that we currently use for KL2 scholars to select these candidates. In fact, KL2 applicants in our prior cycles have included candidates who were very promising but too junior for KL2 funding (see section 3.6.2). This applicant pool will include physicians, nurses, dentists, biomedical engineers or other PhDs who aspire to C/T research careers.
C. Research track residents and fellows will be selected following solicitation for applicants from participating residency/fellowship programs (Table B). The CTSTP will work with each of these programs to help them recruit research-oriented residents and fellows from national pools. Entrants into the participating programs will be encouraged to attend research-oriented professional development activities and to apply to enter the CTSTP with TL1 support.

3.6 Applicant Pools

3.6.1. Predoctoral applicants: Competitive candidates with a commitment to research are recruited nationally to

enter medical or nursing school as dual-degree CTSTP students. Applications are only accepted from training grant eligible (TGE) students, and all applicants in the numbers indicated below are TGE. Most students apply for entry as a dual degree student, but students who develop interests in C/T research after joining the MD or DNP program may also apply to enter the CTSTP. The CCLCM provides a large pool of research-oriented MD students (all do a full year of research with a research thesis). The University Program MD curriculum also requires research experience (minimum four months with a research thesis). Approximately 1 student/year transfers from one of the MD programs to become a dual-degree student in the CTSTP. Some of the DNP-PhD trainees transfer from the DNP program into the DNP-PhD program.

The predoctoral applicant pool reported in Table 6A includes both MD-PhD and DNP-PhD applicants for the 2012–2016 matriculation cycles. MD-PhD applicants to the CTSTP are those who have completed an MD-PhD application and specified interest to enter a core CTSTP PhD program (C/T Science, Epidemiology, Biomedical Engineering, Systems Biology & Bioinformatics) or one of the programs that have C/T areas as a substantial subset of their scope (Cancer, Immunology, Pathology and Genetics, Table A). Other PhD programs that less frequently include CTSTP students are not included in these numbers. Table 6A part I demonstrates a strong and steady applicant pool in the 2011–2016 matriculation cycles, averaging 200 predoctoral applicants/year (all training grant-eligible/TGE). In the last completed application cycle (for matriculation in 2016) we had 271 TGE applicants. This is a large and competitive applicant pool for the number of predoctoral slots available on the TL1.

Table 6A part I shows a mean of 13 new entrants/year to the CTSTP and a mean of 4 new entrants/year appointed to the TL1 (trainees are usually appointed to the TL1 for more than one year, so only a subset of the 11 slots each year are applied to new entrants; these numbers do not include 3 appointments still to be made in the current budget year). While most of the applicants are MD-PhD students, we have had a stream of DNP-PhD applicants that has resulted in five DNP-PhD matriculants (one per year in 2010, 2011, 2012; two in 2015). Table 6A part II shows that CTSTP entrants had a mean of 24 months of prior research experience (21 for new entrants appointed to the TL1). All of the MD-PhD TL1 appointees had at least six months of prior research experience and typically much more. The DNP-PhD students generally had less experience (see plan for improvement, below). Mean GPA was 3.8 for all entrants and 3.7 for appointees to the TL1 over the past five years. All of the applicants and entrants were training grant eligible (TGE; we accept applications only from TGE individuals). Although we encourage individuals with disabilities to apply, no TL1 applicants have reported disabilities. The CTSTP has had success in URM recruiting with 14% URM entrants and 18% URM appointees to the TL1 over the past 5 years (Table 6A, part II). Among all cohorts of current CTSTP trainees (currently or previously appointed to the TL1 grant and listed in table 8A), 19.4% are URM students (Table A). In summary, the CTSTP predoctoral applicant pool is strong in numbers and quality, particularly for the MD-PhD applicants who constitute the majority of entrants.

CTSTP matriculants from 2012-2016 have included 22 new appointees to the TL1 (plus 3 more anticipated appointments still to be made in the current budget year). Since 2007 there have been a total of 55 TL1-supported trainees, including 50 MD-PhD students. The DNP-PhD program has had five matriculants since its launch in 2010; all DNP-PhD entrants have been supported on the TL1 grant.

Future projections: Within the MD-PhD trainee pool, we anticipate continuing strength in the applicant stream with ~13 entrants/year and roughly five TL1 appointees/year with a TL1 support period of about three years (other support sources extend the period of research training). We anticipate that the proportion of engineering students on TL1 slots will decrease as MD-PhD training increases in recently-launched PhD programs (e.g. C/T Science, Systems Biology and Bioinformatics) and in programs in which we have recently launched MD-PhD training through the TL1 (e.g. Epidemiology). In addition, we will continue to support a subset of MD-PhD trainees in the other PhD programs that have C/T emphasis (Genetics, Pathology, possibly others).

Plan for improvement: We will increase both our recruiting efforts and admissions competitiveness (including expectation for prior research experience) to improve standards and outcomes for the DNP-PhD program, even if that means a slightly lower number of DNP-PhD admissions. We will require stronger research qualifications for DNP-PhD matriculation (we will also have increased expectations of students and mentors for publication productivity during the training period; see plan for improvement in section 3.4.4).

3.6.2. Postdoctoral applicants: Postdoctoral training is new proposal for the CTSTP; we do not have current or prior postdoctoral trainees supported on the TL1. We anticipate the following three applicant streams (section 3.5.3):

A. The C/T Science PhD program was just launched in 2015, and we are still expanding its recruitment

activities. We have had two MD-PhD trainees enter this PhD program. Of the 5 other matriculants, 3 hold a clinical doctoral degree and 2 hold an MS degree. All 7 of the C/T Science PhD program trainees are TGE. The applicants all have prior research experience. The postdoctoral or prior-MS entrants had a mean of 3.0 first-authored and 5.8 total publications before matriculation. We anticipate higher numbers of applicants and approximately five entrants/year once recruitment efforts are fully implemented.

B. The C/T research fellowship applicant pool has not yet been actively developed, but the subset of KL2 applicants who were postdoctoral fellows and deemed too junior for KL2 funding represents a conservative starting point for defining this applicant pool. This group has included 31 TGE applicants over the past five years. For example, in the 2014–2015 cycle, we received 10 such TGE applications with a mean of 17.3 publications (range 3-54). There have been no entrants from this applicant pool, as our program has not been designed to accept postdoctoral trainees in the past.

C. Research-intensive residency and fellowship programs (listed in Table B) represent the majority of individuals represented in Table 6B. These programs all require a minimum of 2 years of research time with not more then 25% clinical effort or 18 months full time research. These programs benefit from endowment support and institutional commitments (e.g. the Harrington Physician-Scientist Pathway in Medicine and the Harry Taylor Trainee Awards for Research Track Pathology Residents) – the commitment of the Harrington Discovery Institute and increased recruiting efforts have increased the applicant pool for matriculation years 2014-2016 relative to earlier years, and this component contributes to the trend in total applications for these years shown in Table 6B.

While we have not yet launched the TL1 postdoctoral program, Table 6B demonstrates a strong prospective postdoctoral applicant pool. This is a GENERAL applicant pool from proposed constituent postdoctoral programs of the TL1, NOT actual CTSTP/TL1 postdoctoral applicants, as the TL1 postdoctoral program does not yet exist. Our future TL1 postdoctoral recruitment will restrict applicants to those with substantial prior research experience and publications, and we will target the most competitive of these for entry into the program. The postdoctoral applicant pool for the affiliated programs been 119-159 for matriculation years 2014-2016; increased from 75-90 for matriculation years 2012-2013 (Table 6B, part I); this increase reflects the new institutional commitments (e.g. Harrington and Taylor programs for research track residencies, above) and increased recruiting efforts. The postdoctoral research fellowship request for applications that we will do in conjunction with our KL2 was postponed for the 2016 matriculation cycle and will be completed upon funding of this application; this largely explains the drop in applications from 159 for 2015 to 122 for 2016. The 57 TGE entrants in the last five years had a mean of 2.4 first-author publications and a mean of 4.5 total publications; 13% of these were URM trainees. The size of this applicant pool demonstrates strong feasibility to fill the five proposed postdoctoral slots.

PLAN FOR IMPROVEMENT: When the TL1 postdoctoral program is launched, we will implement higher standards for the TL1 applicants than are demonstrated in the general applicant pool shown in Table 6B. This general pool does not reflect enhanced recruiting and more rigorous standards that will occur for the proposed TL1 postdoctoral program, which will select the most competitive applicants for funding. We will develop URM recruiting efforts as we have done for the predoctoral TL1 program and work to increase diversity and scientific accomplishment of entrants.

3.7. Institutional Environment and Commitment to Training.

Institutional support: CWRU SOM has provided extensive institutional commitment to the CTSTP, including substantial financial support and commitment to develop CTSA educational curricula (e.g. two new PhD programs) that are conducive to C/T research training. Strong CWRU SOM financial support covers many program activities and expenses that are not supported by this grant, including funding for stipend and tuition for C/T predoctoral trainees beyond the number of slots provided by this grant, funding beyond the level of NIH support for trainees on the TL1 (e.g. CWRU SOM supports the grant support shortfalls on stipend and tuition), subsidy of administrative expenses of the CTSTP, including expenses for office operations with three staff, recruiting, numerous programmatic events (retreats, dinner seminars, C/T research luncheon forums and others), travel of faculty and staff leaders to national meetings, student travel to national meetings, and many other expenses beyond the support provided by the TL1 grant. Dr. Harding will have 20% effort devoted to the CTSTP. The other members of the Executive Committee will have the following effort devoted to CTSC research education (TL1 + KL2): Dr. Dweik (20%), Dr. Moore (5%), and Dr. Spilsbury (10%). Approximately one third of total training costs for MD-PhD students are supported by this grant, demonstrating that this grant is highly leveraged and supported by substantial institutional commitment. Dr. Pamela Davis, MD, PhD, Dean of the SOM has provided a letter of support detailing institutional support for the CTSTP.

CTSTP predoctoral trainees (MD-PhD and DNP-PhD) will be supported on the TL1 for up to three years, and the remainder of their research training will be supported from other sources (institutional support, research grants, foundation support, etc.). Thus, TL1 funding will cover less than half of training expenses and will be leveraged with other resources, thereby enhancing the scope and impact of the CTSTP. Tuition support will be supplemented by the School sponsoring the program, and stipends may be supplemented to reach the standard PhD student stipend level for the School. MD-PhD students in the CTSTP and MSTP will be supported at the same level.

Postdoctoral trainees in the C/T Science PhD program will be supported by the TL1 for two to three years, and the remainder of their training period will be supported by their departments and research mentors, leveraging the TL1 support with institutional resources. Postdoctoral trainees in the C/T research fellowships and research-intensive residency/fellowship pathways will be supported on the TL1 for one to two years with the expectation for a research training period of two to three years, or in some cases longer (e.g. as extended in subsequent career stages including a KL2 Scholar phase or other subsequent research career development route). The portions of the training period that are beyond the period of TL1 support for these trainees will be covered by institutional commitments. These come from numerous sources but include endowments (such as the Harrington Physician-Scientist Pathway for research track residents in Medicine, and Harry Taylor Trainee awards for research track residents in Pathology). Departments at CWRU, CC, UHCMC, MHMC and VAMC have provided commitments for trainees in the residency and fellowship programs indicated in Table B.

Other institutional commitments: In addition to direct financial support (above), CWRU (SOM, SOE and SON), CC, UHCMC, MHMC and VAMC all support many faculty efforts that contribute to the CTSTP (e.g. research mentors, the Steering Committee, the Advisory Board, and many faculty efforts for programmatic events); investment in the underlying MD, DNP, PhD, residency and fellowship curricula that contribute to the CTSTP; and the extensive research facilities and programs that support research training of CTSTP trainees.

3.8. Justification of Program Support

Slot number: Our current TL1 grant has 11 predoctoral slots. This application requests funding for 10 predoctoral slots (a reduction of one) and the addition of 5 postdoctoral slots. All of our predoctoral slots have been filled every year; our robust applicant pool substantially exceeds the number of slots available (section 3.6.1). The recent launch of the PhD program in C/T Science in 2015 is already providing applications in this important new CTSTP training program (section 3.6.1). We also have robust applicant pools to the affiliate postdoctoral C/T research training programs (section 3.6.2). In total there were 122 TGE postdoctoral applicants to the affiliated postdoctoral programs in the 2015-2016 cycle. This robust applicant pool will readily exceed the proposed postdoctoral slot number, allowing us to select the most competitive applicants from this well qualified applicant pool.

4. Recruitment and Retention Plan to Enhance Diversity

Commitment to diversity: The CTSTP is strongly committed to increasing under-represented minorities (URMs) in our program. We welcome applications from URMs and those with physical disabilities or disadvantaged backgrounds. The CTSTP actively participates in programs and efforts to improve inclusion, diversity and equal opportunity. The CWRU Office of Inclusion, Diversity and Equal Opportunity (OIDEO) provides strategic leadership for development of policies, procedures and programs to foster diversity and inclusiveness, and The Diversity Leadership Council brings together leaders from many diversity organizations to share insights and promote dialogue; Dr. MacDonald (CTSTP Steering Committee), serves on this committee as an important link for the CTSTP. Dr. MacDonald also coordinates outreach and retention programs and works with Mr. Joseph Williams (Director of Multicultural Affairs, SOM Student Affairs). CTSTP staff, faculty and trainees work to recruit and retain diverse trainees. As of fall 2015, the 972 students in SOM graduate programs included 115 (11.8%) URM individuals (66 African Americans, 48 Latinos, 1 Native American); 55% are women. Among MD students, 9.3% are URMs; 45% are women. Attrition rates are similar for URM and majority students.

CTSTP URM trainee track record: The CTSTP has had success in recruiting URM students: over the last five years 14% of entrants have been URM students (all TGE), and 18% of entrants appointed to the TL1 grant have been URM students (Table 6A). Among all cohorts of current CTSTP trainees (currently or previously appointed to the TL1 grant and listed in table 8A), 19.4% (7/36) are URM students (including 4 African-American and 3 Hispanic students; 6 of the URM appointees have been MD-PhD students, and one was a DNP-PhD student). The percentage of URM trainees among TL1 appointees is higher than that for either our MD or graduate students, demonstrating clear success in TL1 URM recruitment efforts.

Plans: Recruitment and Retention of URM Trainees: We will aggressively pursue URM recruitment. CTSTP

students, the Director, faculty leadership and CTSTP administrative staff will collaborate with Dr. Paul MacDonald and Mr. Joseph Williams to target URM student recruitment by attendance and booths at national and regional conferences focused on URM trainees, e.g. the Association for Biomedical Research Conference for Minority Students (ABRCMS), Student National Medical Association (SNMA), the Latino Medical Student Association (LMSA), and the Society for Advancement of Chicanos and Native Americans in Science (SACNAS). Representatives will also perform campus visits.

We will expand URM recruiting to the new postdoctoral component of the CTSTP. We will add postdoctoral recruiting at national URM forums that we already attend for predoctoral recruitment. In addition, we will recruit at meetings that target physician-scientists in training who will be future research track residency applicants, e.g. the MD-PhD national conference and the American Physician Scientist Association (APSA) meeting (held with the ASCI). URM CTSTP trainees will attend these meetings—we have found that our URM trainees are a great asset in URM recruiting efforts.

URM CTSTP students and SNMA - national leadership accomplishments: CTSTP URM students have important national impact in URM student professional development organizations, particularly the SNMA. CTSTP student DaShawn Hickman is the 2015-2016 National Chair of the SNMA, a major national leadership position. CTSTP student Abner Murray is currently the Co-Chair of the SNMA Diversity Research Committee.

Filling the URM pipeline: In addition to the immediate recruitment of CTSTP trainees during a given recruitment cycle, we seek to expand the pipeline of URM trainees at earlier stages that will then feed into our program and have impact nationally. Our students and faculty will continue to participate in the following programs.

Pipeline 1. High School Programs. The Scientific Enrichment Opportunity Program is an eight-week program for minority and disadvantaged high school students from Cleveland Metropolitan Schools designed to enhance student interest in biomedical and healthcare sciences and provide academic and career mentoring. The Academic Careers for Engineering and Science for Minority Students is a summer research program designed to entice minority and female undergraduate students to pursue research careers. The Joan C. Edwards Summer Research Program provides intense summer research exposure to top minority high school students from the Cleveland School of Science and Medicine. These programs all aim to interest minority, disabled, and disadvantaged youth in careers in biomedical research. Participating CTSTP mentors: Jain, Narla, Stamler.

Pipeline 2. Undergraduate research internships. The NIH-funded Heart, Lung and Blood Summer Research Program engages 12 URM undergraduates and eight URM medical students each year in biomedical research in cardiovascular, pulmonary, hematological and sleep disorders research. The Case CFAR Minority HIV Research Training Program (MHRTP) is designed to recruit and train undergraduate URM research trainees in the HIV/AIDS field. CTSTP mentor participants include in these programs include Gerson, Borawski, Deschenes, Durand, Boom, Letterio, Huang, Kirwan, Jain, Stein, Chance, Wald.

Pipeline 3. Postbaccalaureate training for diverse students. Dr. Paul MacDonald (CTSTP Steering Committee) directs the NIH-funded Case Postbaccalaureate Research Education Program (Case PREP) to support eight URM college graduates in laboratory research, graduate science coursework and preparation for graduate school. Of the 45 PREP Scholar graduates over eight cohorts, 36 (or 80%) have matriculated into top-tier PhD Programs (e.g., U. Michigan, Johns Hopkins, UNC, Vanderbilt, U Penn, Univ. of Washington) with a 3% attrition rate (compared to a 30% attrition rate nationally). Fourteen Case PREP Scholars have entered PhD programs in our SOM, improving diversity in our PhD programs. CTSTP mentors who mentored these students included Subauste, Exner, Abbott, Huang, Cooper, Chance, Jackson, Tesar.

Pipeline 4. The Summer Medical Dental Education Program (SMDEP, funded by the Robert Wood Johnson Foundation) is a six-week summer program to prepare minority and disadvantaged students for careers in medicine or dentistry. The SMDEP enrolls ~80 rising sophomores or juniors per year and is coordinated by Mr. Joseph Williams. The CTSTP Director, Dr. Harding, has provided discussion sessions for SMDEP students to discuss career opportunities in medical research and MD-PhD training.

Retention of URM trainees: The CTSTP actively promotes retention of URM students by close monitoring of URM student progress, individualized advising and help by the CTSTP Director as needed. The CTSTP works with our Minority Graduate Students Organization (MGSO), which holds monthly meetings at which issues of common interest are discussed and students present their research. The MGSO meets with visiting and local minority faculty. The CTSTP also works with the CWRU chapter of the SNMA (the oldest and largest student organization for medical students of color) and the CWRU chapter of the LMSA. In 2015 CTSTP Director, Dr. Harding, met with SNMA and LMSA representatives to plan a Minority Mentor Match Program (MMMP),

including a Speed Mentoring event, resulting in assignment of URM students to URM faculty advisors for long-term mentoring relationships, a URM mentor-mentee mixer, and an MMMP event during our Second Look recruiting revisit program. CTSTP student DaShawn Hickman was co-founder of the MMMP, and Dr. Margaret Larkins-Pettigrew (CTSTP Steering Committee) is the MMMP Faculty Advisor. There are three African American CTSTP students in leadership positions in the MMMP (Hickman, Murray, Ojo).

Recruitment and Retention of Individuals with Disabilities: Among the current and past trainees supported by the TL1, we have not had a trainee with an identified disability, but we have had trainees with disabilities in other CWRU training programs, including the proposed TL1 partner postdoctoral programs. The CWRU Disability Resources Office provides accommodations to enable trainees with disabilities to fully participate in programs and activities, working closely with students to design individually tailored plans for students with a variety of disabilities including visual impairment, hearing impairment, mobility limitations, chronic illness, psychological disorders and learning disabilities. Disabled trainees are provided testing accommodations, adaptive equipment and assistive technology, scheduling assistance, transportation assistance, alternate format for print materials, note-taking assistance, interpreters, parking assistance and accessible housing.

The CTSTP is committed to enrolling students with learning, behavioral, and/or physical disabilities. The CTSTP/MSTP website publicizes our commitment to inclusion and support for disabled trainees; it provides links to institutional support and resources for disabled trainees and applicants. Trainees are offered effective support to accommodate special needs; e.g., extra time to complete exams or assignments, leave of absence for hospital-based care, arrangements with counseling services. Tutoring and additional education support is available. The CWRU Student Disability Services Office has developed resources to educate faculty and others about disabilities (ADHD, learning, chronic illness, behavioral health, hearing and visual impairment, mobility) and to facilitate accommodations for students. Students with disabilities initiate requests for services and accommodations through the Disability Resources office in Educational Services for Students.

Recruitment: The CTSTP will participate in CWRU effort to recruit at universities that serve students with disabilities (e.g., Rochester Institute of Technology, Gallaudet). We will run recruiting advertisements in career magazines for people with disabilities such as Careers & the disABLED. Dr. MacDonald works closely with the CWRU Associate Dean for Disability Resources to develop plans to recruit students with disabilities.

Retention efforts for trainees with disabilities will focus on interaction of trainees with CTSTP leadership (the Director or a Steering Committee member who is well positioned to develop a relationship with the trainee). Students and faculty are encouraged to speak confidentially with the Program Director or a Steering Committee member when a challenge arises. The Director and/or Steering Committee member will work with the student and mentor to develop a course of action, including arrangements for tutorial help, health professional intervention, etc. For MD-PhD students, we will also engage the MD advisor (Society Dean).