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Colorado Clinical and Translational Sciences Institute (CCTSI)

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PROJECT SUMMARY/ABSTRACT

Funded by NIH in 2008 and 2013, the Colorado Clinical and Translational Sciences Institute (CCTSI) at the University of Colorado Denver (CU-D) has taken impressive steps to transform and improve the biomedical; research and training enterprise in the Colorado region and to accelerate and catalyze the translation of discoveries into improved patient care and public health. The CCTSI, a partnership of CU-D, CU Boulder (CU-B), Colorado State University (CSU), six hospitals and 20 community organizations, has established new infrastructure, streamlined processes and expanded existing resources and services for investigators and stakeholders; tripled the number of training and education programs supporting development of a translational workforce; administratively centralized and expanded the breadth of clinical research capacity and expertise; established system-wide informatics capabilities; promoted team science and interdisciplinary research; established an extensive community engagement program and enhanced research across the lifespan; streamlined processes and reduced start-up times for trials; created an academic home for clinical & translational scientists and trainees; and actively engaged in CTSA network activities. Despite these successes, **there remain many challenges to accelerating the translational research process locally and nationally.** This application maps our path forward to meet these challenges. Through 2018 CTSA funding, we will develop new methods, innovations, expertise, and procedures to: a) achieve a new level of measurable performance in training translational teams, b) improve efficiency and quality of the full spectrum of translational research, c) facilitate multi-site clinical trials, d) engage regional communities and stakeholders as partners, and e) collaborate and disseminate best practices into the national CTSA consortium to accelerate the translation of discoveries into improved health and patient care. We will accomplish these objectives by embracing the following five *Overall Strategic Goals*: **Goal 1**: Develop, educate and sustain a diverse translational science workforce to ensure highest research innovation, quality and safety. **Goal 2**: Create a translational research environment in which team science and collaboration both locally and nationally are facilitated, supported and valued. **Goal 3**: Engage local and national communities and stakeholders in all phases of the translational research process. **Goal 4**: Create novel methodologies and resources to support and integrate research in special populations, including children, the elderly, the underserved and those with rare diseases. **Goal 5:** Further innovate and streamline our processes and enhance our informatics capacity for research start-up, implementation and oversight to promote quality, efficiency, & safety of our research and our active participation in the national CTSA Trial Innovation Network. Special efforts will be made to enhance diversity in our workforce. Our progress will be monitored by our Evaluation Core and we will make mid-course corrections as needed to achieve these goals and ultimately improve the health of our state and the nation.

COMPONENT: OVERALL

NARRATIVE

The Colorado Clinical and Translational Sciences Institute (CCTSI) is a collaboration between University of Colorado Denver, University of Colorado Boulder, Colorado State University, 6 hospitals and 20 community organizations aimed at translating discoveries into better public health and patient care. Through a variety of programs, the CCTSI will facilitate the performance of high impact research and the training of the next generation of clinical-translational researchers. Emphasis will be placed on accelerating the pace by which research and clinical trials can be conducted while protecting the safety of research participants in order to bring new effective treatments to patients sooner. Ongoing evaluation of our programs will assure that resources are allocated in a cost-effective manner.

COMPONENT: OVERALL

SPECIFIC AIMS

Funded by NIH in 2008 and 2013, the Colorado Clinical and Translational Sciences Institute (CCTSI) at the University of Colorado Denver (CU-D) has taken impressive steps to transform and improve the biomedical; research and training enterprise in the Colorado region and to accelerate and catalyze the translation of discoveries into improved patient care and public health. The CCTSI, a partnership of CU-D, CU Boulder (CU-B), Colorado State University (CSU), six hospitals and 20 community organizations, has established new infrastructure, streamlined processes and expanded existing resources and services for investigators and stakeholders; tripled the number of training and education programs supporting development of a translational workforce; administratively centralized and expanded the breadth of clinical research capacity and expertise; established system-wide informatics capabilities; promoted team science and interdisciplinary research; established an extensive community engagement program and enhanced research across the lifespan; streamlined processes and reduced start-up times for trials; created an academic home for clinical & translational scientists and trainees; and actively engaged in CTSA network activities. Despite these successes, **there remain many challenges to accelerating the translational research process locally and nationally.** This application maps our path forward to meet these challenges. Through 2018 CTSA funding, we will develop new methods, innovations, expertise, and procedures to: a) achieve a new level of measurable performance in training translational teams, b) improve efficiency and quality of the full spectrum of translational research, c) facilitate multi-site clinical trials, d) engage regional communities and stakeholders as partners, and e) collaborate and disseminate best practices into the national CTSA consortium to accelerate the translation of discoveries into improved health and patient care. We will accomplish these objectives by embracing the following five ***Overall Strategic Goals*:**

Goal 1: Develop, educate and sustain a diverse translational science workforce to ensure highest research innovation, quality and safety

Goal 2: Create a translational research environment in which team science and collaboration both locally and nationally are facilitated, supported and valued

Goal 3: Engage local and national communities and stakeholders in all phases of the translational research process

Goal 4: **Create novel methodologies and resources to support and integrate research in special populations, including children, the elderly, the underserved and those with rare diseases.**

Goal 5: Further innovate and streamline our processes and enhance our informatics capacity for research start-up, implementation and oversight to promote quality, efficiency, & safety of our research and our active participation in the national CTSA Trial Innovation Network.

Common Abbreviations used in this Application

AMC	Anschutz Medical Campus	ACCORDs	Adult and Child Consortium for Health Outcomes Research and Delivery Science	TIC	Trial Innovation Center
BERD	Biostatistics, Epidemiology and Research Design	CTR	Clinical and Translational Research	QPIP	Quality and Process Improvement Program
CBC	Colorado Biostatistics Consortium	CTRC	Clinical Translational Research Center	REDCap	Research Electronic Data Capture
CCTSI	Colorado Clinical & Translational Sciences Institute	CTRE	Clinical and Translational Research Environment Program	RKS	Regulatory Knowledge and Support
CE&R	Community Engagement & Research	CU-B	University of Colorado at Boulder	SARC	Scientific Advisory & Review Committee
CHCO	Children's Hospital Colorado	CU-D	University of Colorado Denver	SOD	School of Dentistry
CLSC	Clinical Sciences Graduate Program	DH	Denver Health & Hospital Authority	SOM	School of Medicine
CMH	Child and Maternal Health Research	DVAMC	Denver Veterans Affairs Medical Center	SOP	School of Pharmacy and Pharmaceutical Sciences
CO-Mentor	Colorado Mentoring Training	EMR	Electronic Medical Record	TEC	The Evaluation Center
COMIRB	Colorado Multiple Institutional Review Board	KL2	Mentored Career Development Program	TL1	Pre-doctoral Research Training Program
CON	College of Nursing	KP	Kaiser Permanente	UCH	University of Colorado Hospital
CO-Pilot	Colorado Translational Pilot Grant Program	KTR	K to R Transition Program	VCHA	Vice Chancellor for Health Affairs
CSPH	Colorado School of Public Health	NJH	National Jewish Health	VCR	Vice Chancellor for Research
CSU	Colorado State University	OGC	Office of Grants and Contracts	TWD	Translational Workforce Development
CTO	Clinical Trials Office	PACT	Partnership of Academicians and Communities for Translation	TIN	Trial Innovation Network
CRAO	Clinical Research Administration Office	I-Corps	Innovation Corps	RIC	Recruitment Innovation Center

COMPONENT: OVERALL

RESEARCH STRATEGY

A. SIGNIFICANCE

THE CHALLENGE AND OPPORTUNITY OF TRANSLATIONAL RESEARCH AT CU DENVER

One of medicine's greatest challenges today is the efficient, seamless and safe translation of biomedical research discoveries into clinical applications that improve human health. New methodologies, technologies and integrated information systems offer unprecedented promise for discovery and growth of translational successes; however significant barriers continue to confound our ability to rapidly move discoveries into clinical practice. These barriers are characterized by the scientific and societal complexities of conducting clinical and translational research (CTR) and the ingrained obstacles in our academic enterprise. Moreover, communities and practices may be hesitant to partner with academic researchers due to historic distrust, unaddressed cultural differences, poor access to clinical services, confusing terminology, and limited experience with mutually beneficial, bi-directional, academic-community collaborations. Consequently, we need to transform translation from an empirical process to a predictive science by developing and testing promising innovations, processes and collaborations that can be disseminated nationally to advance translational science.

To address these challenges and accelerate the pace of research and its translation into improved health, the University of Colorado Denver (CU-D) and its partner institutions established the **Colorado Clinical and Translational Sciences Institute (CCTSI)** in 2008. The CCTSI is today supported by a second round of NIH CTSA funding (2013) and substantial institutional support. The mission of the CCTSI over the past 4½ years has been to transform CTR infrastructure and training at CU-Denver and our partner institutions and institute new efficiencies that will enhance productivity and outcomes. We have established an organizational and operational structure that has instilled a new research culture of interdisciplinary collaboration, has improved and expanded our research infrastructure and or ability to conduct multi-site trials, has broadened “pipeline” training programs and career development opportunities, has created an academic home for clinical and translational scientists across our partner institutions and had forged new collaborations with other CTSAs, with industry and with the communities that we serve. Our Evaluation Core and our Quality and Process Improvement Program (QPIP) undergird a new sense of accountability and continuous improvement, allowing us to make rapid, targeted and rational adjustments in deployment of resources.

Despite these successes, challenges remain and there is more to learn. The NIH formula for calculating CTSA budgets for our 2013-18 grant cycle led to a 42% reduction in our annual CTSA grant funds over the 5 years, yet through improved efficiencies and streamlined infrastructure, institution of a program income system, and new institutional resources, we have managed to retain and enhance all of our important programs without cutting any. However, the costs of research continue to rise and our NIH budget for the next grant cycle will be essentially flat. Because of what we have learned in the last 4 1/2 years, we are ideally positioned to address future budget challenges through further re-engineering of our research processes. In the proposed grant cycle, we will continue to become more efficient and coordinated in our operations to accelerate the clinic study life cycle, integrate special populations across the lifespan into translational research, develop and demonstrate new methods and processes for conducting translational research, optimize our cost recovery for services (with the exception of junior investigators and trainees), further develop our role in the Trial Innovation Network, expand community engagement and partnerships to new groups of stakeholders, develop informatics and technology solutions to advance translation, and develop a diverse highly-skilled translational workforce for the future emphasizing team science and career persistence. As we will demonstrate in this application, CU-D with its 6 health profession schools at the Anschutz Medical Center (AMC), CU Boulder (CU-B), Colorado State University (CSU), our 6 affiliated academic hospitals/health care institutions, and over 20 community organizations are committed to work together to advance translational science and train the next generation of team scientists.

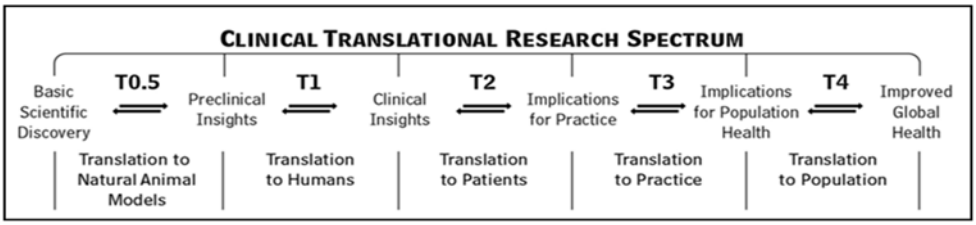
B. VISION AND STRATEGIC GOALS

The ***Vision of the CCTSI*** *is to accelerate and catalyze the translation of innovative science into improved health and patient care*. To achieve this vision, the ***Mission of the CCTSI*** *is to:*

- *Catalyze and enhance scientific discovery, innovation, dissemination and translation across the lifespan*
- *Educate and sustain a resilient, innovative and diverse translational science workforce*
- *Promote and ensure an efficient, safe, collaborative and integrated research environment*
- *Engage stakeholders and communities across the entire translational spectrum*

In short, our mission is to <u>support</u>, <u>connect</u> and <u>train</u> our CTR teams. The CCTSI will continue to support the full range of T0.5 through T4 translational research (Figure 1) in a disease-agnostic manner across the breadth of the life cycle. Through our partnership with CSU, which is recognized for its world class school of veterinary medicine, we will expand the spectrum of translational research to include what we term ***T0.5*** research, translating promising pre-clinical discoveries into naturally occurring animal models (companion to domestic animals) of human disease. We see this as an extremely valuable pathway for establishing proof-of-principle prior to exposing humans to the risks of new diagnostics or therapeutics. CCTSI supports biomedical and biobehavioral scientific disciplines and researchers in all organ-based and public health specialties, across medicine, nursing, dentistry, pharmaceutical sciences and public health and incorporates the expertise of many colleges and schools at the CUD-AMC and downtown campuses, CU-B and CSU. This broad spectrum of research performed is demonstrated by the utilization of our clinical research units in 2016 by over 220 investigators from 27 different research groups or academic units. The CCTSI values inclusivity and collaboration, thus CCTSI Members will include those pursuing important translational questions in the basic and engineering sciences; laboratory and naturally occurring pre-clinical animal models; pharmaceutical and device development; first-in-human trials; pathophysiology and physiologic human phenotyping studies; large scale and multi-site clinical trials (especially those supported by NIH Institutes/Centers); pragmatic/practical clinical trials; community outreach and engagement and community based participatory research; outcomes, implementation and comparative effectiveness research; and public and global health research.

Figure 1. Spectrum of Clinical and Translational research



In this application, we will restructure our CCTSI organization to meet the requirements of the PAR-15-304, re-engineer operations to better promote the highest quality research and safety for both local and multi-site studies and trials, while achieving maximum efficiencies and cost-effectiveness. We will make every effort to integrate CCTSI programs with other institutional research infrastructure to best utilize precious resources and eliminate wasteful duplication. Moreover, sharing our best practices with the National CTSA Consortium and being actively involved in its functions and initiatives is a high priority of each Strategic Goal. ***The following briefly describes our new innovative initiatives to achieve our* Strategic Goals*, with full details provided in the subsequent Components of this application.***

<u>Goal 1: WORKFORCE</u>: Develop, educate and sustain a diverse translational science workforce to ensure highest research innovation, quality and safety.

Ensuring a superbly trained diverse translational research workforce is a major objective of the strategic plan of the CCTSI. Over the past 5 years, our Translational Workforce Development (TWD) education, training, and career development programs have expanded and fortified the clinical and translational research educational and mentoring portfolio at CU-D and its partners, and ensured its alignment with the NIH CTSA Core Educational Competencies in translational research training. *In essence, we have built a clinical and translational <u>educational pipeline</u> that spans the continuum from high school students through our TL1 and KL2 programs to our university leadership, as well as for research staff and assistants*. Thus, we have transformed the educational landscape across the University and our affiliate institutions. In **Components D. Translational Endeavors**, **I. Institutional Career Development KL2** and **J. NRSA Training Core TL1** of this application we will fully describe our educational strategic goals and strategy for achieving them over the next 5 years. **<u>Our TWD strategic goals</u>** are to: **1)** Ensure that the entire CTR workforce receives comprehensive training in Good Clinical Practice, Responsible Conduct of Research, research ethics, and regulatory compliance; **2)** Enhance the CCTSI's workforce effectiveness as teams by providing professional development initiatives in Team Science, Leadership and Mentorship; **3)** Develop, pilot and evaluate a Career Ladder for Professional Research Assistants to standardize professional development and competencies across their career trajectory; and **4)** Close learning gaps identified by the CCTSI Workforce by offering new educational programs in big data/informatics, entrepreneurship, and dissemination and implementation sciences. This will be accomplished under the directorship of Lisa Cicutto, RN, ACNP9cert), PhD, who will also serve as out Liaison to the emerging CTSA network-wide training and staff qualification initiatives. Our Optional Function #2 Innovation Ecosystem (see Component H2.) will employ I-Corps@CCTSI training and other novel programs to promote and support researchers and trainees to form innovation teams with the potential of bringing a biomedical product to market.

Our TL1 and KL2 programs also have a set of strategic goals that synergize with our TWD goals and are designed to use individualized competency-based training methodologies, promote skills in team-based science, entrepreneurship and mentorship, and ensure essential academic skills are achieved in order to produce a diverse, resilient and persistent cadre of CTR scientists for the future. Finally, Dr. Sokol, PI, has already achieved recognition of Team Science in the Promotion Criteria for the CU School of Medicine and he will work with the other health profession schools at the AMC to do the same.

Goal 2: TRANSLATIONAL RESEARCH ENVIRONMENT: **Create a translational research environment in which team science and collaboration both locally and nationally are facilitated, supported and valued.**
The CCTSI has a strong track record of facilitating and incentivizing the advancement of collaboration and team science research both locally and across the CTSA consortium and removing barriers to its performance. Our broad strategic goals are to support inter-disciplinary research collaborations, encourage the appropriate diverse make-up of research teams (e.g., statisticians, clinical trials specialists, pharmacists and gender/racial/ethnic balance), and educate investigators on how to function effectively as a team. In the next award period, we will place an increased emphasis on building meaningful collaborations by embedding community stakeholders in academic research teams. A transformative bold new initiative will be the establishment of a Science of Team Science (SciTS) program to improve the effectiveness and success of team-oriented research within the CCTSI and across the CTSA consortium. In **Component C. Community and Collaboration** of this application we will fully describe our team science and research environment strategic goals and strategy for achieving them over the next 5 years. **Our Translational Research Environment strategic goals** are to: **1)** Expand general team-building and leadership training programs and establish best practices in team science for local and national dissemination.; **2)** Embed community stakeholders in translational research teams; **3)** Implement a Science of Team Science (SciTS) academic program, **4)** support professional development focused on team science and build capacity to help teams apply SciTS knowledge to their activities and **5)** Evaluate the effectiveness of facilitated team-building activities. A few of the novel methodologies we will employ to achieve these goals will include the expansion of our successful Leadership in Innovative Team Science (LITeS) program to now add a LITeS-Lite and a LITeS-Jr. program that will target graduate students and junior faculty, respectively. We will also create a new program designed by Jeni Cross, PhD, a social scientist in the Dept. of Sociology at CSU, that will provide SciTS knowledge and best practices to research teams at CU-AMC through a variety of innovative seminars, workshops, forums and other interactions. The results of these new programs will be carefully and thoroughly evaluated by our Evaluation Core, with continuous improvement of these programs as our objective. Once perfected, the structure and operational details of these new programs will be disseminated to other CTSA Hubs as requested, as has been our experience with demand for implementing our current LITeS program at other CTSA Hubs. We **developed**, modified and finalized the LITeS programming over several years, have **demonstrated** clearly through thorough evaluation its benefit to participants, and are now **disseminating** it to University of Cincinnati and University of Minnesota CTSA Hubs this year. Further details of this CCTSI success story are found in the Collaboration and Multidisciplinary Science section (item C) of **Component C. Community and Collaboration.**

Goal 3: COMMUNITY ENGAGEMENT: Engage local and national communities and stakeholders in all phases of the translational research process.
Community Engagement (CE), with meaningful involvement of community members in our research and training programs, has been a **high priority and a strength** throughout the 9-year lifespan of the CCTSI. We have demonstrated the value and benefits of engaging patients and communities as **active partners** in the full spectrum of CTR to address priorities of community members, design studies in a culturally-sensitive and participant-friendly structure, implement and disseminate findings into the community, and enhance public trust and participation in research. The CCTSI has built a robust CE infrastructure governed by the **Partnership of Academicians and Communities for Translation (PACT) Council**, aided by 8 Community Research Liaisons (**CRLs**) embedded in diverse racial, ethnic and geographic communities around Colorado and partnered with the Colorado Foundation for Public Health and Environment (now Trailhead Institute), which assists the CCTSI in building research infrastructure in our partner communities. Our CE and Research (CE&R) Core, built on the Governance of the PACT Council, includes Educational Programs, Longitudinal Community Relationships, Consultation Services, Boot Camp Translation, Community Immersion experiences and a CE Pilot Grant Program. These programs are conceptually joined as a pipeline of resources designed to serve investigators and community members seeking to improve community health through translational research. In the next 5-yr grant cycle, the CE&R Core will broaden the stakeholders with whom we engage and further integrate CE&R throughout the breadth of the CCTSI, our partners in team science at CU-D, CU-B, CSU, our hospital partners

and the CTSA Consortium. In **Component C. Community and Collaboration** of this application we will fully describe our community engagement goals and strategy for achieving them over the next 5 years. **Our CE strategic goals** are to: **1)** Expand our community stakeholders to include the array of healthcare organizations and payers to expand the potential for implementation and dissemination; **2)** Further infuse CE throughout the translational spectrum within all CCTSI programs and operations; and **3)** Increase capacity for bi-directional engagement between researchers and community stakeholders to enhance the science of community-engaged translational research. These goals will be achieved through enhancing existing successful programs and creating new initiatives. For example, we will create a Stakeholder Advisory Board of health care organization partners that will meet with PACT Council regularly to explore opportunities for expanded partnerships, advise on potential new collaborative opportunities and assist bringing PACT activities to a broader group of stakeholders. The CE&R core will also now integrate more fully with our Regulatory Knowledge and Support Core, Administrative Core, TWD program and TL1 and KL2 programs, Informatics Core and our Trial Innovation Network Hub Liaison Team, in order to infuse community member input into our operations and planning, and to promote community engagement principles throughout the CCTSI. The effect of these new interactions will be evaluated by Evaluation Core. Details about these new integrations are found in the individual components of this application.

Goal 4: LIFESPAN AND SPECIAL POPULATIONS: Create novel methodologies and resources to support and integrate research in special populations, including children, the elderly, the underserved and those with rare diseases.

The integration of special populations (ISP) across the lifespan in CTR is critical for building the foundation of knowledge on which evidence-based medicine can be practiced, and to better understand the early origins of disease, the factors that promote disease development and progression at various life stages, and the potential age-specific effectiveness of therapeutic strategies aimed at prevention or treatment. Similarly, CTR must include underserved segments of the population to advance knowledge of how cultural, socioeconomic, and other factors influence health. In the next award cycle, the CCTSI will build from our extensive experience and broad programs in research directed at infants and children, pregnant women, the elderly, underrepresented minorities and rare diseases, and provide new resources to expand and promote lifespan research. In **Component F. Hub Research Capacity (ISP)** of this application we will fully describe our ISP goals and strategy for achieving them over the next 5 years. In addition, **Component H1. Optional Function #1 Early Life Exposures (ELEP**) of this application will focus further on our initiatives in child and maternal lifespan research. **Our ISP strategic goals** are to: **1)** Ensure that infants, children, and adolescents continue to be an important focus of CTR within the CCTSI by supporting research in both common and rare diseases. Some new approaches will be to engage members of the community and Patient Advocacy Groups (PAGs) as research partners and to catalyze new ideas through the CMH Pilot Grant program. **2)** Evaluate and promote the appropriate inclusion of older adults in CTR; some approaches will be to use OnCore (our CTMS) to track inclusion of older adults in CTR, establish an Aging Research Working Group to examine issues related to age bias and inclusion or exclusion of elder adults in CTR, and to support two unique ongoing national research networks based at CU-D for end-of life care and for disabled elderly in long-term facilities. **3)** Develop a standardized approach for monitoring recruitment success in CTR protocols and strategies to enhance the inclusion of underrepresented minorities; we will set up OnCore to be used to capture accrual rates and facilitate reporting of URM enrollment and retention so that CCTSI can identify and work with underperforming research teams to improve their performance. Furthermore, we will make available new local recruitment tools or those from the Recruitment Innovation Center (RIC) of the TIN to reach hard-to-reach populations. Finally, we will work with our CE&R program and its Bootcamp Translation and CRL programs to improve community-based recruitment (see Component C. Community and Collaboration).

Goal 5: STREAMLINING AND QUALITY IMPROVEMENT: Further innovate and streamline our processes and enhance our informatics capacity for research start-up, implementation and oversight to promote quality, efficiency, & safety of our research and our active participation in the national CTSA Trial Innovation Network.

Critical Strategic Goals in this grant application are to improve and streamline our processes and methods to ensure that research performed at CU-D and partner institutions is of the highest quality, that barriers are identified and overcome, that we accelerate study protocol approval, start-up, implementation and completion, that we maximize efficiency in our operations and the conduct of clinical trials, and that the safety of human research participants is of the highest priority. Sections **B. Evaluation and Continuous Improvement** and **C. Quality and Efficiency** in **Component A. Administrative Core** will provide more details. **Our goals for**

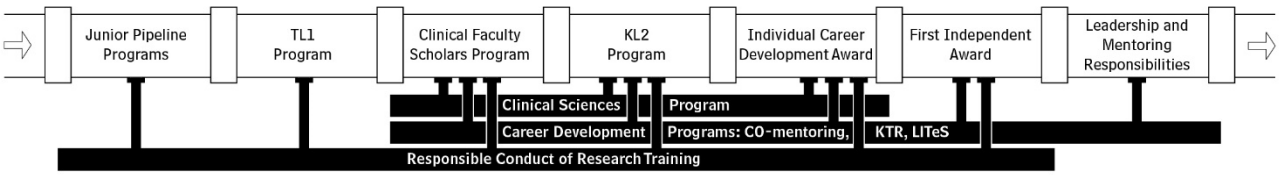
Streamlining and Quality Improvement are: **1).** We will ensure high quality research by expanding CCTSI scientific review of proposed study protocols beyond those protocols requesting CCTSI resources. Our CTRC scientific review committee (SARC) will provide review of all patient-oriented non-peer reviewed research protocols prior to submission for IRB review, campus-wide. We will provide highly trained and certified research personnel at our state-of-the-art clinical research facilities (CTRCs). A new Clinical Trial Management System (OnCore) will be fully implemented for all clinical research by 2018-19, integrated with our EMR (Epic) and used by our CRAO and RKS programs to track progress of each clinical trial from planning through review and study start-up through completion. Details of these initiatives are in the **RKS section of Component E. Research Methods** and **PCI section of Component G. Network Capacity**. **2)** We will initiate a Study One-Stop Support (SOS) conceptual program that will be a seamless integrated pathway from study development through publication and dissemination of results. The SOS will integrate across many of the CCTSI Cores and Programs to reduce duplication, remove barriers, and provide the investigator with a logical and streamlined pathway for clinical research and trials performance. SOS is described in detail in the **Quality and Efficiency section of Component A. Administrative Core. 3)** To maximize our efficiency and effectiveness of research we will further develop our Quality and Process Improvement Program **(QPIP)** that complements our **Evaluation Core**. Bethany Kwan, a health outcomes and comparative effectiveness investigator at CU-D with expertise in LEAN system redesign and quality/process improvement, will now direct QPIP, which will map and redesign processes to become more efficient and eliminate unnecessary variation in procedures, and reduce cost. The Evaluation Core team is comprised of Ph.D.-credentialed evaluation professionals who collectively bring more than 4 decades of experience with conducting large-scale evaluations for NIH, NSF, CDC and the U.S. Department of Education. The team includes evaluators with specialized quantitative and qualitative expertise who have applied their skills to develop rigorous quasi-experimental designs, engage in policy analysis, and support broad-based organizational change and capacity-building initiatives. Details about QPIP and the Evaluation Core are in Component A. Administrative Core of this application. **4)** A principal objective of the CCTSI is to simplify, accelerate and support the process for approving, implementing, enrolling and completing NIH-funded multi-site clinical studies and trials. The CCTSI has extensive experience in supporting NIH multi-site trials through our CTRCs, however the processes for study, budget and contract approval and study implementation have been tedious for many investigators. Therefore, we are excited to become part of the Trial Innovation Network of NCATS to provide new resources and support to our research teams through the TICs and RICs. In this regard, CU-D has signed on to the ACTA agreement to speed contract negotiation, signed the SMART IRB agreement to participate in single/central IRBs, and we are in the process of developing our Trial Innovation Network Hub Liaison Team (see **Componen**t **G. Network Capacity** for details). Through our TIN Team, RKS, BERD, Informatics and CE&R cores and programs, we will plan to provide new study design and regulatory support to assist investigators in preparing and completing IRB and budget submissions and more rapid study start-up, enrollment and completion. Our institution is committed to participate in the TIN and the Central IRB model for multi-site studies; to further streamline our processes to achieve rapid IRB and contracting approval, and to work with the RICs to achieve improved participant recruitment and study enrollment.

C. TRACK RECORD IN TRANSLATIONAL AND CLINICAL RESEARCH

CU-D and the CCTSI affiliated partner institutions share a rich history of innovations in clinical and translational sciences that have advanced human health and patient care. The following will enumerate **some of our high impact contributions over the past 5 years** that have advanced research towards better methods, processes and ultimately human health, based on the 5 strategic goals outlined in PAR-15-304.

1. Workforce development: The CCTSI has emphasized workforce development programs to ensure that the entire translational science workforce has the skills and knowledge necessary to advance translation of discoveries (details in Components D., I. and J.). CCTSI has built a comprehensive and integrated pipeline of educational programs for attracting, training and retaining a highly competent workforce, which has been fully

Figure 2. Education & Career Development Pipeline iic Persistence



integrated with our TL1 and our KL2 programs. Our educational pipeline approach (**Figure 2**) for scientists facilitates synergies in efficiencies, coordination of efforts, and reduce redundancies.

Several of the many **high impact achievements in Workforce Development** over the last 5 years are:

- **CO-Mentor** (See Component I. KL2, B.3.2.5): Mentorship is a critical factor contributing to the success and persistence of junior CTR investigators. Goals of CO-Mentor are to develop skills and behaviors for effective mentoring relationships. CO-Mentor consists of four half-day sessions for mentor-mentee dyads, occurring each 7 weeks during one year that address the following: career mapping and interpersonal communication skills; understanding financial aspects of an academic career: negotiating percent effort for research, education, clinical, and administration; managing project budgets; and salary support/funding portfolio;, improving goal setting skills; and applying a conceptual framework for making personal work choices that promote academic growth and persistence. CO-Mentor has consistently achieved high levels of participant satisfaction from mentors and mentees. Mentees reported benefits in the following areas: 95% agreed/strongly agreed that they had greater clarity regarding their career and development needs and 91% of mentees were more confident that they could successfully establish mutually-agreed upon goals and expectations with a mentor. Mentors reported the most significant gains in providing coaching (p=0.001), developing and reviewing a personal career development plan (p=0.002), identifying strengths and gaps in the mentoring team (p=0.004), and intentionally working to achieve a satisfactory work-life balance (p=0.001).

- **I-Corps@CCTSI** (see Component H2. Innovation Ecosystem, C.5): I-Corps is a team-based immersive innovation learning program taught by faculty with an entrepreneurial background, which prepares teams to compete for SBIR/STTR funding. I-Corps@CCTSI launched in 2016 at CU-AMC after we were chosen competitively as one of 10 NCATS funded sites. We are expanding the program to CSU in 2017. To date we have trained 19 teams representing a spectrum of T1 to T4 innovation. I-Corps@CCTSI is a 3-week introductory short-course to help teams identify their target customer and through a customer discovery process involving 30 interviews test their "value proposition" hypothesis. Our first group of teams gave this program high marks in our initial evaluation of the program and we will pursue expansion of I-Corps in this grant application.

- **Clinical Research Education Program (CREP)**: To ensure that the entire CTR team has the skills and knowledge for clinical studies and trials, a curriculum was developed to improve regulatory knowledge and compliance and GCP and RCR application. CREP provides required regulatory courses (GCP, RCR, human subject protection including informed consent) for all personnel at CU-AMC involved in CTR through a variety of use-friendly training forums: seminars, courses, individual consults, online modules. The RKS Core oversees this program that reaches over 700 attendees annually.

- **Leadership in Innovative Team Science (LITeS):** (see Component C. Community and Collaboration) LITeS is a comprehensive year-long program to promote effective leadership in building productive research teams. It is composed of four 2-day sessions over one year with 30 completing it each year. Following the program, over half of participants reported applying their learning a great deal of the time. 70% indicate enhanced social capital, network reach, and connectedness to the institution, resulting in a new strength in leadership of team science by senior faculty.

- **K to R and Pre-K Mock Grant Review programs**: (see Component I. KL2, B.3.3.) To improve grant writing skills and success for junior faculty, these mock study sections were instituted over the past 5 years, and held in the 2-month interval before each NIH grant application deadline to provide assessment and input to allow time for application revisions. Expert reviewers are solicited across the CU, CSU, and CCTSI affiliates based on the topics in each application. What sets our process apart from others is that applicants, mentors (if appropriate) and reviewers <u>all</u> attend the mock study section for the corresponding grant review and mock study section. The study section is organized like a standing NIH panel, apart from the fact that the applicants (and mentors, if applicable) are present for the discussion and all submissions are discussed. After proposals are reviewed, the chair requests comments/insights from participants and the applicant is permitted to respond to criticisms, or ask questions. The Pre-K Program (for K01, K08 and K23 grants) has reviewed 77 applications since 2014. Our overall applicant success rate for funding of 48% is higher than the national average of 30% for K awards and more than $12M dollars in grant support has been awarded. For the K to R program, 16% of reviewed grants were funded within 1 year while 25% were funded within 2 years. Importantly, over 46% of participants received some type of independent research funding within a year of program participation with grants totaling $67 million. Our success rates demonstrate the effectiveness of the program, which exceeds the national rate of 15% for the same time frame. Qualitative feedback from participants, mentors and reviewers is overwhelmingly positive.

- **Clinical Science Graduate Program (CLSC):** (see Component I. KL2, B.3.1.1) One of the first of its kind in the nation, CLSC is the CU-D degree (Masters and PhD) granting program for advanced training in CTR. The CLSC has been expanded over the past 5 years to now be the second largest graduate program at CU-D. This program is truly interdisciplinary and strongly promotes team science and socialization through innovative methods, including having students participate in collaborative real-world assignments, review one another's work (grants/proposals, data collection tools, etc.), hold debates, and give presentations. Over the past 4 years, the CLSC program graduated 14 PhD and 47 MSCS students. Currently 78% of CLSC alumni (MSCS=62; PhD=57) hold grant support with 55% and 45% of PhD and MSCS graduates, respectively, holding a federally-funded grant as a PI or Co-PI in the past 4 years. In total, our alumni have held over 370 grants in the last 4 years, over 670 grants since graduation, and have published over 2,500 peer-review manuscripts in high impact journals such as Pediatrics, JAMA, Circulation, and Cancer.

2. Collaboration/Engagement: The CCTSI has developed arguably some of the most comprehensive collaboration, team science and community engagement programs in the CTSA consortium, with many of our programs being adopted by other CTSA Hubs. Our PACT Council structure for CE&R has resulted in a model for community-academic partnerships. Some of the notable high impact achievements over the past 5 yrs are:

- **Boot Camp Translation (BCT**). (see Component C. Community and Collaboration). BCT addresses the final translational barrier, by taking evidence-based guidelines and recommendations and converting them from scientific, medical language into messages that are accessible and understandable to patients and community members. The participation of community members in developing this messaging is key to the success of BCT in changing behaviors. BCT has been used for >30 medical topics in Colorado and throughout the U.S., with CCTSI, PCORI, & AHRQ funding; 4 BCT facilitator trainings have been held in Colorado, and in Oregon and Saskatchewan. A 2016 invited paper in *Health Affairs*, describes BCT's role in completing the final step of translational research to the community and practice level.

- **Community Research Liaisons (CRLs)** are a unique link between CU-AMC and communities. CRLs provide essential support to our CE&R activities and community health initiatives while educating both investigators and community members about the value of equitable and participatory research partnerships. CRLs are embedded in the communities they serve and have a unique understanding of their community's assets and challenges. CRLs engage local patients and health providers to identify community health priorities and assist investigators in designing locally relevant studies that address real community, partner, patient and health provider needs. By employing CRLs that are embedded in their communities, we have developed a new type of community outreach for research that is highly effective.

- **Community Engagement Consults** (see Component C.) provide expert consultative support for investigators who wish to engage communities in research. Our Community Consults & Ethics Committee, with 13 community and academic members, meets monthly to discuss ethical concerns in community-engaged research and provides consultation to investigators and research teams. These consults have been particularly effective for assistance with PCORI grant applications. One notable consult in 2016 was with our new CU Center for Personalized Medicine, helping to create a Community Advisory Board that will now be a bedrock of this genomics program

3. Integration: We have emphasized and promoted the integration of special populations across the lifespan in translational research from our first CTSA grant application in which we proposed a Child-Maternal Health special function. Our pediatric and perinatal CTRCs (clinical research units at CHCO), among the busiest across the CTSA consortium, facilitate performance of research during pregnancy and delivery and in newborns, infants, and children of all ages, supporting over 200 active research protocols and thousands of annual research visits. The availability of CTRCs and other CCTSI resources are in a large part responsible for the ranking of the CU SOM Department of Pediatrics #1 in NIH funding in 2016 for pediatric departments. Groundbreaking work over the last 5 years in cystic fibrosis, type 1 and type 2 diabetes, HIV/AIDS, obesity and metabolic syndrome, cancer, genetic and metabolic diseases, organ transplantation, rare liver and lung diseases, chronic viral hepatitis, celiac disease, schizophrenia, autism and many other conditions was only possible because of the CTRC experienced staff and facilities. Our Perinatal Research Facilitation Committee, which reviews requests for new studies during pregnancy, determines feasibility and assists investigators in crafting proposals that can be accomplished within the desired timeframe, maximizing the use of already collected data and specimens in our repository. Our CMH Pilot Grant program has funded over 25 studies which have yielded over 7:1 return on investment in follow-on grant funding, allowing for detailed investigation of important pediatric medical problems. Over the last 5 years,

a stronger emphasis on early life exposures and the developmental origin of adult diseases research in the CCTSI has led to increased investigation of the effects of maternal obesity and hyperlipidemia on a variety of clinical outcomes of their infants, brain development and cardiovascular health (reviewed in **Component H1. Early Life Exposures Program**). Numerous investigations by Dr. Wendy Kohrt and colleagues examined exercise, muscular and bone health in the aging adult and their impacts on outcomes, all conducted within the adult CTRC at UCH. We have made available an exercise research laboratory and DXA adjacent to the UCH CTRC to allow for easy and accessible investiga-tions of energy metabolism and function in elderly adults (**see ISP section of Component F. Hub Research Capacity**).

4. Methods/Processes: The CCTSI has identified barriers in our enterprise that impeded the efficient and effective conduct of CTR, and we have developed new methods and streamlined processes to overcome these roadblocks and accelerate processes for approval and start-up of studies. Several of the many **high impact achievements in Methods/Processes** over the last 5 years are:

- **Centralized IRB:** The Colorado Multiple Institutional Review Board (COMIRB) at CU-D was one of the first centralized IRBs in the nation (since 1991), and has expanded its agreement between CU, CHCO, CSU, NJH, University of Northern Colorado, CU-D, and NJH to function as a single IRB, with authorization agreements with >160 separate institutions. In the last 3 years, COMIRB has become the IRB of Record for several large Practice-Based Research Networks associated with the CCTSI Community Engagement & Research Pillar Program. COMIRB and the CCTSI are active participants in IRB Share, have signed onto SMART IRB, and have new infrastructure in place to cede reliance to central IRBs, including the TICs of the Trial Innovation Network.

- **Establishment of CRAO:** In 2016, CU-D transformed and centralized our campus clinical research support infrastructure by designing and constructing a new space to house the re-engineered consolidated Clinical Research Administration Office (CRAO). The new integrated shared space is open-concept, "Google style" to facilitate frequent interaction, communication and dynamic problem solving. The teams from UCH and CU-D (**Table 1)** moved into this new space in early January 2016 and it has greatly enhanced communication, efficiency, problem solving and streamlining of our processes.

Table 1. Research Services of CRAO

Pre-Approval Process	Operations	Post-Approval
Portal submission Affiliate review Scientific review of protocols Budget negotiation Feasibility assessment Coverage analysis Pricing Facilitation FDA submissions Clinicaltrails.gov registration	Contracting Contract facilitators MTA facilitators Central IRB facilitator Regulatory facilitator CTMS calendar and budget builder CTMS training	Research billing Recruitment assistance CTMS reports Clinicaltrials.gov data entry Facilitate data sharing Study monitoring Regulatory audits Training support Study close-out and evaluation

- **Clinical Trials Management System (CTMS):** Historically, the CU-AMC and CCTSI affiliates have had a fragmented and decentralized approach to clinical research management with little visibility to anyone but the individual study team. CU-AMC in collaboration with UCHealth have transformed this paradigm, by implementing a CTMS (OnCore) in 2015 that will provide the backbone infrastructure for clinical trials across CU-D and the UCHealth system. Over 1500 Cancer Center and 300 other protocols are in the system, with the goal for complete migration in 2018.

- **Centralized Scientific Review:** The Scientific Advisory and Review Committee (SARC) has historically performed scientific and feasibility review of new research protocols proposing to use services or facilities at one of the 5 CCTSI CTRC units. To improve and standardize the quality and safety of all investigator-initiated, non-peer-reviewed clinical research at CU-D, SARC's role was expanded in 2014 to perform scientific review of all such protocols that have not already undergone external peer-review (whether CTRCs are used or not) that were submitted to COMIRB to ensure that all research is of the highest scientific quality and is to be conducted safely and ethically. This has reduced the burden on COMIRB reviewers and sped up the process for protocol approval by COMIRB.

5. Informatics: (see **Component B.**). Informatics at CU-D has become the backbone of our CTR enterprise and, as such, has undergone a dramatic transformation over the past 5 years. Some of the high impact achievements that allow for CTR data acquisition, sharing, transfer, analysis and security are:

- **Health Data Compass (HDC) Research Data Warehouse**: Responding to the strong recommendation of the CCTSI EAC reports which highlighted the lack of a Big Data strategy at CU-Denver, a transformational event was the creation of **Health Data Compass** in 2015 which has become the clinical and translational research data hub for the CU-AMC campus and the emerging Big Data analytics programs at CU-D. Dr. Michael Kahn,

CCTSI Informatics Director has overseen this implementation. In 2017, HDC will complete its migration to Google Cloud Platform, the *first* integrated large-scale genomic, clinical, administrative, and population-based data warehouse implemented in this platform, proving to be an exciting innovation-enabling architecture and public-private partnership..

- **Colorado Center for Personalized Medicine (CCPM).** In 2014, a $63M joint investment by the UCHealth System, CHCO, the CU SOM and CU Medicine established the CCPM, which hosts two notable translational informatics resources -- the *Translational Informatics and Computation Resource* (TICR), a high-performance computing cluster for genomic sequencing and bioinformatics; and *Health Data Compass* (HDC), a multi-institutional research data warehouse. Similar data warehouses, data networks, and data governance activities have been deployed over the past 5 years in CCTSI-affiliated institutions (Kaiser Permanente Colorado, Denver Health and National Jewish).

- **Colorado Health Observation Regional Data Service (CHORDS)**. A Denver metro regional data sharing network (https://goo.gl/7sBm1v), CHORDS was created in the past 5 years and has provided data to public health stakeholders and clinical researchers using the HSCRN VDW CDM and the PopMedNet distributed query system, borrowing technologies and governance from both HSCRN and PCORnet, where 3 CCTSI affiliate organizations are active participants. Geocoding, spatial population-level analytics, and map-based visualizations are widely used in the CHORDS data network. Funded by the Colorado Health Foundation, a community and stakeholder based governing board composed of technical and data partners, researchers and surveillance stakeholders oversee data stewardship, partnerships, and appropriate data use.

D. INTEGRATION OF HEALTH CARE AND RESEARCH

Coordination between the health care delivery system and the CTR enterprise is essential to ensure that information about research studies is accessible, understandable and timely to both patients and clinicians so that appropriate patients can be made aware of research studies and invited to participate. With the advent and now ubiquitous nature of the electronic health record (EHR), the CCTSI and its affiliate partner hospitals, most of which are using Epic as their EHR, will embark on several coordinated initiatives listed below to bring both the patient and the busy clinician into the CTR team in a seamless, simple and compliant fashion.

1. We will integrate the research data and clinical study lifecycle into clinical care practice and in patient-centered venues at our hospitals, clinics and virtual spaces. The traditional separation between clinical research, clinical care, and online media is being replaced by integrated processes for research participant identification (e.g., i2b2 and ACTA), outreach and recruitment, e-consenting, e-source data collection, automated study compliance, patient-reported outcomes, and safety monitoring. The University of Colorado Hospital (UCH) currently exchanges basic patient information via real-time messaging between Epic's EHR and Forte Research's OnCore CTMS and key clinical variables with the AgileMD clinical decision support engine for complex predictive modeling and integrated order sets. With most patients seeking information on clinical trials thru online resources, the CCTSI partnered with TrialSpark (www.trialspark.com), a patient recruitment start-up that generates tailored trial recruitment messages to targeted social media sites to engage hard-to-recruit patient populations. We will expand linkages between operational systems, research systems and external systems, including social media-based communications platforms linked to clinical and research management systems, to create seamless data flows across care, home and personal settings.

2. With our hospital system IT and research operational leadership, we will establish joint governance and procedures to identify and prioritize real-time patient recruitment alerts within the Epic EHR for both clinicians and in the patient EHR portals (e.g., My Chart). We will align this effort with existing EHR-clinical decision support governance and institutional consent and regulatory oversight to enable provider and patient-oriented trial eligibility alerts in normal clinical and patient portal workflows. We will follow best-practices to minimize alert fatigue and patient enrollment burden. This functionality exists within the Epic platform; however, the governance and oversight of recruitment alert programs require a well-thought out policy and oversight committee structure such that patients and providers are not overwhelmed by alerts. We will also be engaged in a wide-spread educational and communication campaign describing the roll-out of these new initiatives for clinicians and their staff as well as patients.

3. We will create bidirectional EPIC and OnCore data exchange interfaces to enable exchange of coded clinical trial eligibility parameters and study-specific safety triggers, using implemented web services and FHIR interfaces. We will partner with operational health IT teams and commercial clinical decision support vendors,

such as AgileMD, to modify existing web-services-based real-time patient identification methods that detect patients for guideline-based care to include trial eligibility triggers. We will expand existing oversight procedures for requesting, approving, and implementing clinical documentation changes that embed study-specific structured data capture into the operational workflows.

4. We will encourage investigators to incorporate innovative social media recruitment and eHealth data capture services via TrialSpark and other commercial partners by providing start-up funds for new studies to use these services. We will collect metrics to assess the impact of social media methods on recruitment times and eHealth applications on patient-entered data capture rates.

5. We will establish an EHR-Research Best Practices Collaborative Working Group with our affiliate institutions. This group will foster bilateral exchange of successful technical, governance, and evaluation practices for introducing research workflows into local EHR systems. Four of our CCTSI partner institutions have installed Epic although each system supports institution-specific workflows and have different IT oversight structures. We will be active participants in CTSA-wide EHR-Clinical Research Integration activities supported by the CTSA Informatics Domain Task Force and CD2H. In this manner, we will learn from our CTSA Hub colleagues and bring best practices back to our institution.

6. We will work with UCH and CHCO to develop a mechanism by which patients at time of hospital or clinic registration can opt-in or opt-out of agreeing to be contacted about future research studies, essentially a research registry. Some of our affiliates (e.g., NJH) have such a process in place. Interestingly, UCH may want to take a different approach, i.e., have an honest broker identify potential research participants for a given study through the Health Data Compass data warehouse, notify the patients about the study that they are eligible for, and obtain permission to have the study team contact the patient, if they are interested. CHCO is likely to approve in 2017 the registration to be contacted approach (opt-in) for children seen at CHCO facilities. If the two hospitals choose different mechanisms to achieve patient notification, we will study the outcomes of these two processes, as outlined in Component E. Research Methods, item B. Innovation.

E. WORKFORCE DIVERSITY

RECRUITMENT AND RETENTION PLAN TO ENHANCE DIVERSITY

CU-D and its affiliate institutions are committed to efforts to increase the diversity of our CTR workforce at all levels. CU-D believes that a diverse faculty and research staff will foster innovation and creativity, contribute to the learning environment, improve the quality of the researchers, advance the likelihood that underserved or health disparity populations will participate in, and benefit from, health related research, and build public trust and community partners in the research enterprise. Moreover, the CU-SOM believes that a diverse student body enhances excellence in medical education and practice, and **provides the pipeline for future CTR investigative teams**. A primary diversity goal of CU-SOM is to increase the matriculation of students from backgrounds underrepresented in medicine (URM). In the following we will outline current diversity data and the describe efforts of the CCTSI and CU-D to **identify barriers for success and create solutions**, thereby increasing the diversity of students, faculty, staff and other members of the CTR workforce at our institution.

A. Student Diversity

Current Data: CU SOM has increased the number and percentage of URM students over the past 7 years. The class of 2013 had only 13 URM students while the **class of 2020 has 51, and class of 2021 has 50** (out of class of 186). Data also show that enrollment of URMs in SOM Residency Programs has more than tripled, based on race and ethnicity, over the past 10 years. In 2007, the proportion of URM trainees was 3% and in 2013 it doubled to 6% and **for 2017-2018 it will be 10%**. Therefore, the various efforts listed below to advance diversity in this important pipeline to CTR investigators have been successful in recruitment, however attention needs to also be paid to barriers for success

Table 2- SOM	First-Year Students	All Students	Employed/ Full-time Faculty	Senior Administrative Staff
Black/African American	9 (5%)	31 (4.5%)	25 (1%)	3 (1.8%)
Hispanic/Latino	23 (13 %)	94 (13.7%)	86 (4%)	2 (1.2%)
American Indian/Alaska Native	10 (6%)	21 (3.1%)	7 (< 1%)	0 (0%)
Native Hawaiian/Pacific Islander*	1 (0.6%)	4 (0.6%)	not available	not available
Vietnamese	9 (5%)	58 (8.5%)	not applicable	not applicable
Citizen raised in rural area	20 (11%)	48 (6.9%)	not applicable	not applicable
First-generation college student	39 (21.5%)	not available	not applicable	not applicable
Low socioeconomic status	66 (36.5%)	not available	not applicable	not applicable
Asian	not applicable	not applicable	187 (8%)	7 (4.3%)
Female	not applicable	not applicable	1,822 (53%)	61 (37.6%)

* Native Hawaiian/Pacific Islander is included with Asian individuals as a diversity category for faculty and senior staff.

(see below). **Table 2** presents the diversity data for the 2016 first year SOM class, all students and the SOM full-time faculty. In 2017, >50% of faculty are women.

CU-D Programs. CU-Denver's Office of Diversity and Inclusion (ODI), under the direction of Chief Diversity Officer and Vice Chancellor for Diversity and Inclusion, Dr. Brenda J. Allen, is promoting diversity through a wealth of programs and opportunities at CU-D and the AMC, including expanding educational opportunities for URM high school and undergraduate students that will strengthen the URM pipeline into our TL1 program and the SOM. The Office of Inclusion and Outreach (OIO) directed by Dominic F. Martinez at the CU-AMC has the mission is to promote and support a diverse community that acknowledges values, fosters, and benefits from the unique qualities, rich histories, and wide variety of cultural values and beliefs that mirror and fulfill the CU-D AMC mission. The URM pipeline of partners, termed SUMMiT (Summer Undergraduate Minority Mentoring in Translational Science**),** includes programs at Dine College (Navajo tribal college, Spero Manson MD), CU-AMC, CU-Denver, and CU-B. *We anticipate a higher percentage of URMs in the health sciences in future years as our URM Pipeline Programs mature in attracting exemplary URM students to clinical and translational science*. The SOM and School of Dentistry have one-year Post- Baccalaureate programs designed to recruit and support URM students, whose academic background made them a higher risk for admission in medical school.

SOM Programs. The Office of Admissions, working in close collaboration with the CU-SOM Office of Diversity and Inclusion (directed by Shanta Zimmer, MD), the Office of Student Life, the CUSOM Diversity Council, the CU-Denver vice-chancellor for Diversity and Inclusion, and other partners, has developed additional outreach and pipeline programs to identify and admit qualified underrepresented and disadvantaged students interested in medicine. CUSOM provides mentorship, preparation, academic support, and career advising to high school, college, and post-baccalaureate students through numerous programs (details on SOM website http://www.ucdenver.edu/academics/colleges/medicalschool/administration/diversity) including: *BA/BS-MD Program*, *Colorado Rural Health Scholars Program (CORHSP)*, *Pre-Admission Workshop (PAW)*, *Pre-med workshops*, *GEMS-HP*, *Colorado Undergraduate Summer Research Program*, *and the Medical Scientist Training Program.*

B. Translational Research Workforce and Faculty Diversity.

Current Data: We collect racial, gender and ethnicity data as individuals become Members of the CCTSI, which is required to use CCTSI resources.. Based on over 4,250 current Members (which include faculty, post-docs, research associates, & trainees), the % of URMs in our Translational Research Workforce (**Table 3**) has grown substantially over the 4 years of the current grant cycle, although still have not reached our goals of equaling the Colorado population diversity.

Table 3 - CCTSI Diversity

CCTSI MEMBERS	2017	2013
Women	51%	45%
Hispanic/Latino	8%	3%
Asian	7%	4%
African-American/Black	3%	1%

SOM Programs: Over the past 5 years major SOM efforts have been undertaken to **identify and address barriers** to recruiting and retaining URM faculty and to increase the diversity of the CU SOM faculty, most of which spend a portion of their time conducting research. The 2015 SOM Diversity Plan provides an overall roadmap for promoting an inclusive climate and for recruiting and retaining faculty members, administrative leaders, students, and residents. The SOM Diversity Council provides strategic guidance to the dean and other leaders and assists in monitoring progress toward the school's diversity goals. Members of the council include faculty, deans, medical students, administrators, funding and development leaders, and community representatives. For high-level administrative leaders, searches are guided by the CU-Denver vice-chancellor for Diversity and Inclusion and the CUSOM associate dean for Diversity and Inclusion, one of whom serves on each search committee. The vice-chancellor and associate dean also provide search committee training ranging from formal seminars on unconscious bias to specific interventions. Individual departments also have access to training and information on techniques and best practices for identifying and attracting a wide range of candidates, including women, racial and ethnic minorities, LGBT individuals, and those with disabilities**. The Dean of CUSOM further encourages departments to recruit diverse faculty members through tangible salary support (0.25 FTE) and resources (individualized).**

The SOM provides **mentorship and faculty development services** for those in school-identified diversity groups and has established policies to ensure an atmosphere that fosters diversity. For example, the academic promotion and tenure standards specifically recognize and reward SOM faculty members for activities that promote community engagement, pipeline programs, community-engaged scholarship, and participation in activities that promote diversity and improved care for underserved patients and populations. The SOM Diversity Plan includes guidelines on preventing the isolation of minority faculty within the institution and helping underrepresented faculty identify role models and mentors. The Diversity Plan also warns against the "minority

tax"—additional responsibilities placed on underrepresented faculty to achieve minority representa-tion. The *University of Colorado Organization for Racial and Ethnic Support (UCOLORES)* was established in 2010 to provide a "safe place" for underrepresented faculty, staff, students, and residents. UCOLORES identifies barriers by promoting open and honest dialogue about differences in backgrounds and ideologies, the importance of diversity in the mission of the institution, and strategies for fostering an inclusive climate. Groups meet monthly and are led by a steering committee and mentored by the CU--D vice-chancellor for Diversity and Inclusion and the SOM associate dean for Diversity and Inclusion. The *Women in Medicine and Science Committee* supports, encourages, mentors, and helps prepare women throughout the academic medical community. The committee hosts networking events, career development workshops, and orientation materials for all levels of faculty, house staff, and students. The *Lean In CU – Women in Medicine and Science* is a peer mentoring group to facilitate the success of women at the Anschutz Medical Campus. Other groups and activities include the dean's New Minority Faculty Support Fund and opportunities available through the Centers for American Indian and Alaska Native Health.

C. CCTSI-specific programs: The CCTSI is engaged with all of the CU-D and SOM programs listed above to address increasing URM participation as researchers, staff and students, identifying barriers to success and developing and instituting solutions. We have also taken special efforts to identify and address barriers for URM participation in our TL1 and KL2 training programs to ensure success and persistence in an academic career for a diverse group of researchers and their teams (see **Components I. and J**., section C. for extensive description of these efforts) and in our Community Engagement programs (**see Component B**.)

D. Research Staff and Community-Campus Partnership. The workforce involved in translational research goes well beyond students, faculty and scientists, and involves those in allied health professions, study coordinators, facilitators, community research liaisons and others. The Anschutz Medical Campus is located in the heart of one of Colorado's most economically challenged and underserved regions. Original Aurora and the other neighborhoods surrounding the campus have some of the highest rates of health problems and greatest health needs in the state. Given the increasing evidence that poverty is the root cause of health and educational disparities, it is nearly impossible to improve health and education outcomes without addressing these root causes. The CU-AMC Community-Campus Partnership is identifying opportunities for improving the economic well-being of local residents. This partnership led to The Hire Local Program which is designed to increase the number of Original Aurora residents employed on the Anschutz Medical Campus and facilitate coordination and enhancement of career pathway ("pipeline") programs on the campus, which in turn will increase the diversity of those involved in the translational workforce. The AMC vision for the Hire Local Program is to serve as a central point of contact for all local residents, especially underrepresented residents, to access information, services and programs related to jobs on Anschutz Medical Campus. The goals of this program are: 1) To increase the number Aurora residents employed on the Anschutz Medical Campus, 2) To identify careers in health sciences, facilities, office support and other entry-level opportunities that exist on the campus and 3) To facilitate coordination and enhancement of career pathways ("pipeline") programs and activities on the campus. The initial pipeline program is the Healthcare Bridge Job Pipeline Program which is a full-time, 10-week training program through the Community College of Aurora (CCA), in partnership with the CCP, where students learn the skills needed to be better qualified for specific health-related jobs while receiving college credit – at no cost to them. Students receive specific training from instructors from Children's Hospital Colorado and University of Colorado Hospital in order to enhance pipeline opportunities for the graduates to those employers. Additionally, students are assigned to a Workforce Specialist who assists in their post-graduation transition for an entire year, including job searching, job readiness, crafting résumés based on what employers are expecting, and learning effective interviewing skills. We will encourage the program graduates to enter our research workforce through our close working relationship with the Director of the Community-Campus Partnership, Robert McGranaghan, MPH, a former PACT Council member of our Community Engagement & Research Core Program.

E. Research Nursing and Study Coordinators. Expanding the diversity of our research nursing staff, study coordinators and professional research assistants is also a high priority of the CCTSI. One pipeline to these staff positions is the CU College of Nursing which believes that Diversity among nursing faculty clinicians and the education of diverse students enhances the diversity of the future health care workforce. We will work with the College of Nursing to provide research nursing as an option for their students, URM and others, by holding formal presentations and informal meetings with students, as well as rotations in our research units. In addition, we will make all efforts to hire URM research nursing staff for our CTRCs, especially those that are bilingual or were raised in Colorado communities that were underserved.

COMPONENT A: ADMINISTRATIVE CORE

PROJECT SUMMARY/ABSTRACT

The CCTSI was created in 2008 at CU-D as an institute with the authority and broad reach to forge relationships within the CU system and with outside partners, communities, affiliated hospitals, and industry. The Director/PI of the CCTSI, Dr. Sokol has programmatic authority and autonomy to implement the programs and functions of the Institute, manage the space assigned to the CCTSI, and hire and fire personnel within the Institute. Collaboration has been obtained from CU-D, CU-B and CSU leadership, the Deans of each health profession school, CEOs of each Affiliate Hospital and Health Care Organization, community organizations,, corporate leaders, officials at each campus, and most importantly, the faculty, investigators and trainees. The organizational structure for the CCTSI provides an infrastructure to support a broad range of T0.5 to T4 research activities across the partnering institutions and as the foundation for training and developing the next generation of clinical and translational workforce. The over-arching goal is to provide a robust and supportive governance structure and research environment to enable and ensure high quality, highly efficient, cost-effective and compliant research to flourish at our institutions. An outstanding leadership group who have worked together for a number of year is proposed. There is close integration among all functions, with themes of community engagement, use of informatics and technology, collaboration and communication permeating throughout the entire CCTSI organization, as will be demonstrated in the individual sections of this proposal. The **Specific Aims** are to: **Aim 1**) Provide an integrated Organizational Governance Structure that engages participating institutions and constituencies to promote the vision of the CCTSI; **Aim 2**. Develop processes for Evaluation and Continuous Improvement that ensure responsive tracking of metrics, assessment and evaluation*;* **Aim 3***.* Promote a system-wide approach to ensure the highest Quality, Efficiency and Safety in the entire clinical study life cycle, and **Aim 4**. Disseminate successful solutions to translational barriers locally and throughout the CTSA Consortium. Continuous quality and process improvement will be emphasized, communication and collaboration among the partner institutions will be promoted and valued. In collaboration with our Evaluation Core, Common Metrics and local metrics will be established and reported to monitor progress and evaluate potential areas of focus for the CCTSI quality and process improvement team. CCTSI will work closely with the Clinical Research Administration Office (CRAO) at CU-D to ensure study quality, participant safety and operational efficiencies during the entire study life cycle. Our Dissemination Core will perform consultations and provide educational materials to bring best practices in dissemination of medical advances to our communities.

COMPONENT A: ADMINISTRATIVE CORE

SPECIFIC AIMS

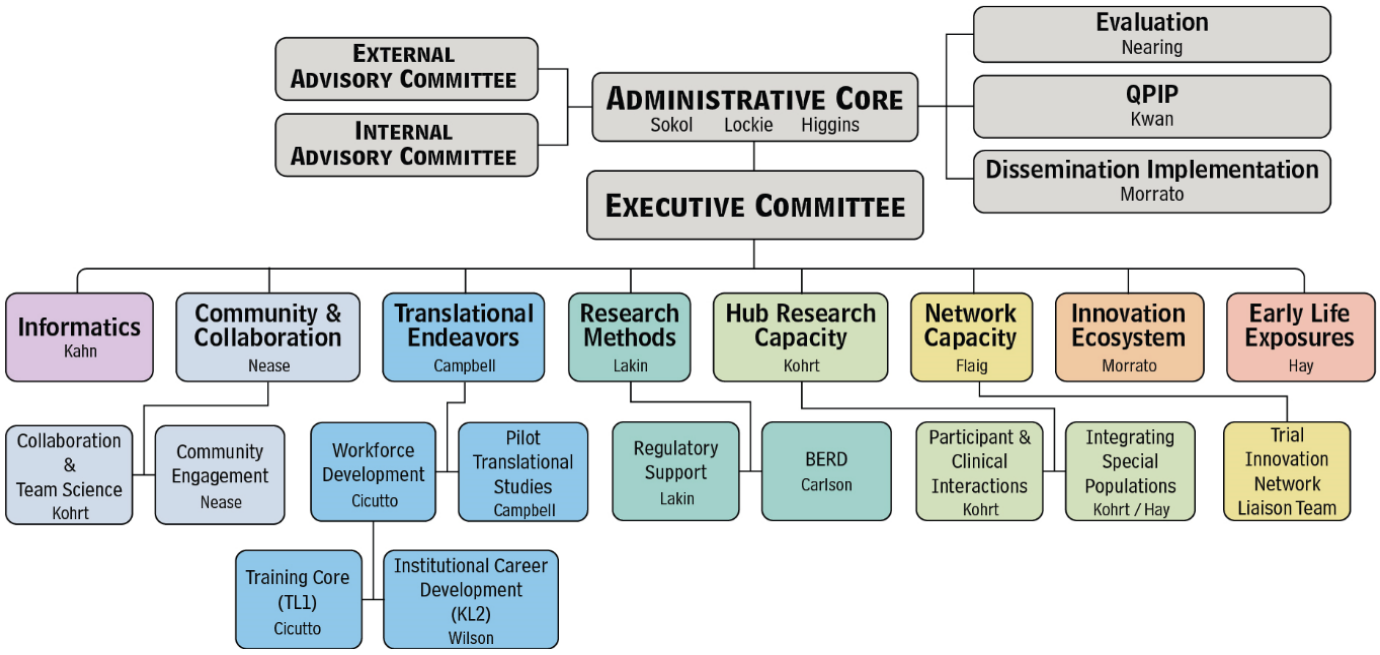
The Organizational Structure for the CCTSI (**Fig. 1**) provides an infrastructure to support a broad range of T0.5 to T4 research activities across the partnering institutions and as the foundation for training and developing the next generation of clinical and translational workforce. The over-arching goal is to provide a robust and supportive governance structure and research environment to enable and ensure high quality, highly efficient, cost-effective and compliant research to flourish at our institutions. *Although the organizational structure separates the CCTSI functions, there is close integration among all functions, with themes of community engagement, use of informatics and technology, collaboration and communication permeating throughout the entire CCTSI organization, as will be demonstrated in the individual sections of this proposal..*

The purpose of this section is to detail the innovations and inclusiveness of the administrative structure for the CCTSI that is distinct from but integrated into the infrastructure of the various partner institutions. *Each specific aim corresponds to one of the 3 subsections outlined in PAR-15-304 plus an additional section on Dissemination & Implementation.* The **Specific Aims** are to:

1. **Provide an integrated Organizational Governance Structure that engages participating institutions and constituencies to promote the vision of the CCTSI.**
2. **Develop processes for Evaluation and Continuous Improvement that ensure responsive tracking of metrics, assessment and evaluation.**
3. **Promote a system-wide approach to ensure the highest Quality, Efficiency and Safety in the entire clinical study life cycle**
4. **Disseminate successful solutions to translational barriers locally and throughout the CTSA Consortium.**

The CCTSI is a collaboration of University of Colorado Denver (CU-D), CU- Boulder (CU-B), Colorado State University (CSU), 6 hospitals/health organizations, and 20 community organizations with the common goal to accelerate translation of discoveries into improved health and patient care. A robust Administrative Core is therefore needed to promote collaboration, communication, quality, efficiency and continuous improvement across all entities. In collaboration with our Evaluation Core, Common Metrics and local metrics will be established and reported to monitor progress and evaluate potential areas of focus for the CCTSI quality and process improvement team. Our overall aim is to ensure that all federally-funded and other research (including multi-site studies) is conducted to the same high standards of quality and safety, and as efficiently as possible. We will disseminate our demonstrated innovations to our local teams and across the CTSA consortium.

Figure 1. Organizational Structure of CCTSI



NOTE: Commonly used abbreviations in this section are defined in the Overall Section of this application.

COMPONENT A: ADMINISTRATIVE CORE

RESEARCH STRATEGY

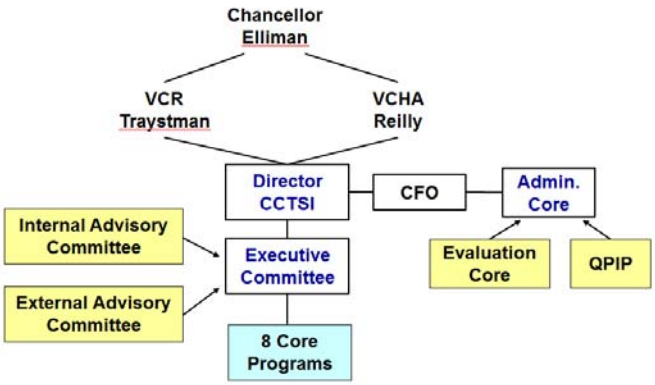
1). ORGANIZATION, GOVERNANCE, COLLABORATION AND COMMUNICATION. ***Specific Aim 1: Provide an integrated Organizational Governance Structure that engages participating institutions and constituencies to promote the vision of the CCTSI.***

A. SIGNIFICANCE. The CCTSI was created in 2008 at CU-D as an institute with the authority and broad reach to forge relationships within the CU system and with outside partners, communities, affiliated hospitals, and industry. The Director/PI of the CCTSI, Dr. Sokol has programmatic authority and autonomy to implement the programs and functions of the Institute, manage the space assigned to the CCTSI, and hire and fire personnel within the Institute. Buy-in has been obtained from CU-D, CU-B and CSU leadership, the Deans of each health profession school, CEOs of each Affiliate Hospital and Health Care Organization, community members (*see Letters of Support),* corporate leaders, officials at each campus, and most importantly, the faculty, investigators and trainees. The CCTSI is actively involved in identifying barriers and finding solutions, introducing new software and technologies and establishing data sharing infrastructure and agreements that have transformed the Colorado biomedical enterprise and its relationship to communities throughout the state. The CCTSI provides the highest quality research support services, state-of-the-art facilities, pilot funds and workforce development programs used by a diverse group of investigators across our partner institutions.

B. APPROACH

B.1. Organizational Structure. The CCTSI has been a formal Institute since 2008 within the CU, based at CU-D Anschutz Medical Center campus (AMC), and governed by an Executive Committee chaired by Ronald Sokol, MD, the Director and Principal Investigator in the current application The Director reports to the Vice Chancellor for Research (VCR), Richard Traystman, PhD, and the Vice Chancellor for Health Affairs (VCHA), John Reilly, Jr. MD, the Dean of the School of Medicine, who in turn report to the CU-D AMC Chancellor, Donald Elliman, Jr., who oversees the campus of the AMC and all of its Schools and programs (**Fig. 1 & 2**). The Deans of the other health sciences schools report to the VCHA. The VCR and VCHA work closely to integrate and support educational, research and clinical programs at AMC, thus the dual reporting of the CCTSI Director to both of these individuals will ensure the campus-wide integration of CCTSI programs.

Figure 2. Reporting Structure of CCTSI



The ***PI/Director*** (Dr. Sokol) will have institutional responsibility and authority for all aspects of the implementation and function of the CCTSI and will have daily involvement with the activities of the CCTSI, including: 1) oversight of all administrative, strategic, academic, operational, and financial functions, 2) control over assignment of space and allocation of resources assigned to the CCTSI, 3) relationships with the partner institutions, 4) collaboration with other CTSAs through the National CTSA Consortium , 5) interaction with NIH NIH Program Officer, and 6) maintenance of career development opportunities to encourage new investigators in clinical and translational sciences. The PI/Director will work with Department Chairs throughout the Health Profession Schools at CU-D, and appropriate departments at CU-B and CSU, to help recruit outstanding investigators and ensure their protected time for research, and with ensure promotion of investigators. (Note: The CCTSI does not have authority to directly hire faculty, who must have an appointment within a department within a school or college). The PI/PD is viewed as the campus leader in CTR research and training and sits on important committees at CU-D, including the Executive Committee of the SOM, the Clinical and Translational Research Advisory Committee to the VCR and VCHA, the Enterprise Data Warehouse planning committee, the Research Advisory Forum at UCH, Research Institute Scientific Committee at Children's Hospital Colorado (CHCO) among others. The PI/PD will be an established well-funded clinician scientist who is a recognized academic leader at CU-D, with a funded research program, excellent administrative, fiduciary and communication skills, highly regarded by the partner institutions, and with extensive experience in translational research infrastructure and training programs.

The CCTSI ***Administrative Director/Chief Financial Officer*** (Tim Lockie, MS, MBA) will work closely with the PI/Director to prepare the budget for each year; oversee our program income system; oversee day to

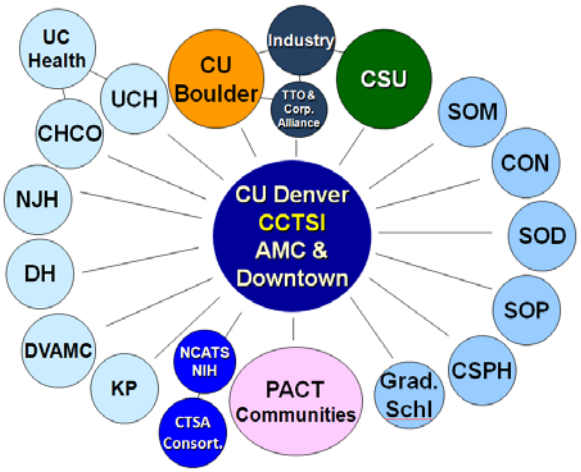
day fiscal management and monitor expenses and program income; ensure compliance with institutional and federal grants management policies and principles; generate fiscal and other required reports, direct CCTSI human resources; manage the administrative, financial and operational teams; attend monthly meetings of Department/Division/Centers Administrators; direct the monthly CCTSI Administrators meeting; prepare annual NIH progress reports; coordinate the preparation of the annual non-competing continuation applications, participate as a member of the CTSA National Consortium Administration KFC and attend annual meetings; and direct the Administrative Core.

The CCTSI functional units are organized into **8 Core Programs** which have been realigned to match the Core Functions outlined in PAR-15-304 (**Fig. 1**), each of which will be overseen and managed by a CCTSI Associate Director who reports to Dr. Sokol, and is responsible for the functions, implementation, and oversight of their Program. Each Core Program may contain several Cores, to better address the strategic goals outlined in Overall Component. Each Core Program will have a Steering Committee chaired by the Associate Director which will meet monthly or bimonthly; administrative staff will be assigned to each Core Program.

The **Executive Committee (EC),** chaired by the PI/Director, will meet each 2 weeks for 1-2 hours to review progress of CCTSI operations, integrate activities and operations across the 8 Core Programs and across the partner institutions, approve pilot grant funding, review challenges that have arisen and obstacles that have been identified and assist the PI/Director in problem-solving, and discuss evaluation of the program. The EC will include the 8 Associate Directors, 5 other Core Directors, the Trial Innovation Network (TIN) director, the Quality and Process Improvement Program (QPIP) director, the Evaluation Core director, one research leadership representative from CSU, CU-B and CHCO, and the Administrative Director. The EC will function as a team, as they have during the past 9 years and during the planning process of this application, and will serve as ambassadors of the CCTSI on and off campus. In addition, the EC will work with the Evaluation and QPIP programs to implement process improvement and efficiency measures. The presence of leadership of each of the main CCTSI functional units at the EC meetings will promote effective communication, integration and collaboration across the Institute. An **Internal Advisory Committee** of school/college leaders and active researchers provides input to the PI and the EC on important issues.

B.2. Partner Institutions and Stakeholders. The CCTSI, based on the AMC of CU-D, has become the academic home for clinical and translational investigators and sciences at the 4 largest Colorado public research university campuses (AMC, CU-D Downtown, CU-B, & CSU), 6 academic hospitals and health care organizations, and over 20 community organizations and PBRNs located throughout Colorado (**Fig. 3**). The academic institutions and hospitals are located between Downtown Denver and Aurora, with the exception of CU-B (25 minutes away) and CSU (60 minutes away). These Colorado institutions and communities have collaboratively achieved success over the past 40 years in promoting excellence in education and training in all health care professional fields and in cutting-edge research programs. The first 9 years of the CCTSI program transformed and solidified the academic and training relationships among these institutions. Each university has extensive health related academic programs with substantial research funding and have collaborated together for years on major NIH Center grants, program projects and other research programs (**Table 1**). The academic hospital partners include University of Colorado Hospital (UCH) and CHCO (both located on the AMC but neither owned by CU-D), National Jewish Health (NJH), Denver Health (DH), Denver Veteran Affairs Medical Center (DVA) (to be located on the AMC in 2018) and Kaiser Permanente Colorado (KP). In the following we provide a **brief description of our partner institutions and stake-holders**. *A **full description** of each partner institution, their attributes and important roles in the CCTSI is provided in **Facilities and Other Resources.***

Figure 3. CCTSI Participating Institutions



B.2.1. CU-D and Partner Research Universities

- **University Of Colorado Denver (CU-D)** is a comprehensive University within the region's largest metropolitan area, with a Downtown Denver Campus and the Anschutz Medical Center Campus 9 miles east in Aurora, CO. With more 12 schools and colleges, CU-D awards more than 3,400 degrees each year and more graduate degrees than any other institution in Colorado. The **Downtown Denver Campus** is the most ethnically diverse college campus in Colorado, providing opportunities for improving minority and underserved population

participation in training. **AMC,** the only Academic Health Center within the state of Colorado, is the central location of the CCTSI and is home to the 6 health profession schools. CU-D research and training *grant awards exceeded $437 million in FY 2016 with $206 million received from NIH* (**Table 1**). *The Chancellor of CU-D and the Deans of each CU Health Profession School have provided Letters of Support.*

Table 1. CCTSI Partner Universities and Health Profession Schools/Colleges

University or School	Location	# Faculty	# Students	2016 Grant Funding (NIH)
CU Denver AMC-Aurora	AMC	4403	3,694	$430 million ($201 M NIH)
Medicine	AMC	3437	1529	$333 million ($174 M)
Nursing	AMC	143	911	$4.7 million
Pharmacy	AMC	123	657	$15.2 million ($12.7 M)
Dentistry	AMC	122	317	$4.5 million ($3.7 M)
Public Health	AMC	115	583	$32 million ($10.7M)
Graduate School	AMC	NA	774	$0.21 million
CU-D Downtown	Downtown	1412	14,271	$35 million ($5 M)
CU Boulder	Boulder	2844	31,861	$435 million ($46.3 M)
Colorado State University	Ft. Collins	1560	33,198	$320 million ($33.5 M)
TOTAL		8,735	77,315	**$1.22 billion ($285.8 M NIH)**

The AMC is home to the **CU School of Medicine (SOM)**, one of the outstanding public medical schools and research institutions in the United States. SOM houses the NIH-funded CU Comprehensive Cancer Center, a working partner of the CCTSI with many shared resources. The **CU College of Nursing (CON)** is the premier nursing school in the Rocky Mountain West and is best known as the birthplace of the nurse practitioner, and for research in community outcomes, informatics, and human caring. CON trainees and faculty will have major involvement in the Clinical Science PhD graduate program, informatics and the Community Engagement and Research activities of the CCTSI. The **CU Skaggs School of Pharmacy and Pharmaceutical Sciences (SOP)** is consistently ranked among the top pharmacy graduate programs and ranked 5th in NIH funding in 2016. The school has developed a cutting-edge Medicinal and Translational Pharmacology Program. The **CU School of Dentistry (SOD)** is the preeminent dental school within the Rocky Mountain West Region. The School pioneers research in oral cancer, Native American oral health, salivary gland disease, neurobiology, pain control and tissue engineering. The **Colorado School of Public Health (CSPH)** created in 2007 is a partnership between CU-D, CSU and University of Northern Colorado. The CSPH plays a major role in the training programs and T3 and T4 translational research programs within the CCTSI, and houses the CCTSI Biostatistics (BERD) Program. **CU-D Graduate School** offers 21 PhD graduate programs and five Masters Programs. PhD degrees may be obtained in multiple basic and clinical science fields (including the Clinical Science PhD program). The **CU-D, Downtown Denver Campus** is a comprehensive urban university which offers bachelor to doctoral degrees in the full spectrum of liberal arts and professional fields. The School of Education and Human Development houses our Evaluation Core.

- **University Of Colorado At Boulder (CU-B)** is a premier academic and research University, including 8 schools and colleges and 44 doctoral degree programs. With 5 Nobel Laureates on the faculty, there is a rich history of innovative discovery leading to human applications in fields of biotechnology, medical research, biochemistry, biology, and engineering. *Grant awards exceeded $435 million in FY 2016 with $332 million received from federal sources.* Interdisciplinary collaboration between CU-B and CU-D investigators has led to major discoveries in bioengineering, tissue engineering, congestive heart failure, congenital heart disease, the microbiome, pharmaceutical biotechnology, and molecular biology. A CCTSI CTRC is located at CU-B. One of the major CCTSI goals will be to expand collaborative interdisciplinary research and training programs between CU-B and CU-D. *The VC of Research has provided a letter of support.*
- **Colorado State University (CSU)** is a public land grant institution founded located in Fort Collins, one hour north of Denver. CSU includes 8 colleges and over 30,000 students, including the renowned College of Veterinary Medicine and Biomedical Sciences (ranked in top 3 nationally). CSU is considered one of the leading research universities in animal sciences, atmospheric science, infectious diseases, and environmental science and with total *grant awards exceeded $320 million in FY 2016*. Collaborative research and education programs have taken place for decades between CSU faculty and CU-D and CU-B faculty. CSU is a partner in the CU Comprehensive Cancer Center (NCI), the Nutrition and Obesity Research Center (NIDDK), and the CSPH, with major CU-D research collaborations in infectious disease, exercise physiology, HIV/AIDS research, community engagement and research. CSU partnership in the CCTSI will expand the use of Natural Animal Models of human diseases. *The Vice President of Research has provided a letter of support*.

B.2.2. Hospital And Health Care Organization Partners. NOTE*: All researchers at the following hospitals have faculty appointments at CU-D.*

University of Colorado Hospital (UCH), located on the AMC, is a private, not-for-profit hospital (not owned by CU) for adults and is one of the primary teaching hospitals for CU-D. UCH is consistently ranked among the top hospitals in the country by *US News and World Report*. Facilities include a 600 bed hospital, the Anschutz

Outpatient Pavilion (550,000 outpatient visits annually), and the Anschutz Cancer Center. UCH is dedicated to research and quality improvement in clinical care. CCTSI CTRCs are located at UCH. Will Cook, UCH President, gives his full support to the CCTSI and CTRCs (*see Letter of Support*).

University of Colorado Health System (UCHealth). Created in 2011, this *largest health system* in *Colorado* combines UCH with 5 other hospitals in Colorado and Wyoming, totaling over 1,500 hospital beds and >1.3 million outpatient visits. Unprecedented opportunities for expanding clinical trials, personalized medicine and community-based research will unfold over coming years as a single electronic medical record (Epic) is operational installed in all of the hospitals. The CCTSI will play a major role in developing and integrating clinical research infrastructure, data sharing and training across UCHealth.

Children's Hospital Colorado (CHCO), one of the preeminent academic pediatric healthcare institutions in the nation, is a private, not-for-profit independent hospital with a strong affiliation with CU-D. CHCO, consistently ranked in the top 10 Children's Hospitals by *US News and World Report*, relocated to its 1.4 million ft^2 facility at AMC in 2007, putting it in close proximity for the first time to the health science schools, UCH, and the CU-D training and research facilities. Total beds are 444 and there are > 500,000 outpatient visits annually. The CHCO CTRC is one of the most active in the nation. Jena Hausmann, President and CEO of CHCO, has pledged her support to the CCTSI (see L*etter of Support*).

National Jewish Health (NJH) is known world-wide for ground-breaking basic and translational research and treatment of respiratory, immune, and allergic disorders. NJH is a non- sectarian, not-for-profit academic hospital which has been ranked #1 in respiratory diseases for 19 consecutive years by *US News and World Report*. NJH and CU-D collaborate extensively on training and research, with shared fellowships, co-investigators on grant applications, and shared core facilities. A CCTSI CTRC unit and Core Lab facilities have been housed at NJH for the past 23 years. Michael Salem, MD, President and CEO of NJH, has pledged his ongoing support to the CCTSI (*see Letter of Support*).

Denver Health (DH), a premier safety net hospital, provides healthcare for over 25% of all residents in the City of Denver. DH is a comprehensive, integrated health care organization, including a 477 bed hospital, the Denver Public Health Department, an 11-site network of school-based health centers in the Denver Public Schools, correctional care, and a 9-clinic network of family health centers throughout Denver. DH faculty of the SOM have been international leaders in trauma and surgical research, health outcomes research, community translational research and informatics technology, and HIV prevention and treatment. Robin Wittgenstein, the President and CEO of DH, has committed partnership and support for the CCTSI (*see Letter of Support*).

Denver Veteran's Affairs Medical Center (DVAMC) is a training site for CU-D residents in all adult specialties. The DVAMC will relocate in 2018 to a new 182 bed 1.1 million ft^2 facility on the AMC, bringing the three major CU-D teaching hospitals to the same campus for the first time. Supported by *over $58 million of grant funding*, DVAMC conducts major clinical and translational research in cardiovascular epidemiology, gastrointestinal cancer, chronic hepatitis, mental health, neurodegenerative diseases, diabetes, substance abuse and geriatrics. DVAMC faculty hold leadership positions within the CCTSI. Sallie Houser-Hanfelder, Director of DVAMC, has pledged continued CCTSI partnership (*see Letter of Support*).

Kaiser Permanente of Colorado, Institute for Health Research, (KP), directed by Claudia Steiner, MD, Professor of Medicine, is the research arm of KP in Colorado, and employs over 120 investigators & staff receiving *over $20 million of extramural funding* for projects that focus on advancing preventive health and improving process and health care delivery. KP investigators hold appointments in CU SOM. Roland Lyon, President of Kaiser Foundation Health Plan-Colorado, has committed support to CCTSI (*See Letter of Support)*

B.2.3. Community Organizations And Partnerships. Through the CCTSI Community Engagement & Research (CE&R) program, sustained relationships with over 30 community organizations have been established. The Partnership of Academicians & Communities for Translation (PACT) is the governing body of the CE&R program and is a statewide collaborative of academic researchers, community-based organizations, PBRNs and healthcare provider networks working together to provide a platform for innovation in CE&R. The PACT is governed by a 16 member Council, meeting quarterly, with equal representation from communities and from the academic institutions. Among the PACT members is the Shared Network of Colorado Ambulatory Practices & Partners (SNOCAP), which includes 7 large PBRNs which cover the state of Colorado and have performed over 80 research studies. PACT organizations cover nearly 300 physician practices, 30 hospitals and one million individuals, representing rural, underserved and minority populations.

B.2. Integration of CCTSI with Partner Institutions. Theoretically, one might expect the existence of major disparities in institutional culture among the CCTSI partner institutions that would create competing institutional perspectives and would be a challenge for implementing a CTSA Hub across 4 university campuses and 6 academic hospitals. However, in reality these ***institutions have worked collaboratively for decades*** and are

well aligned in missions and actions. For example, all research and clinical faculty in each of the 6 hospitals are faculty in the CU SOM, Pharmacy, Public Health, Dentistry or Nursing, as CU-D is the only AHC with health profession schools for 500 miles. Thus, scientists interested in research have sought and received appointments at CU, regardless of their hospital affiliation, for 40 years. Establishing a central IRB (COMIRB) on record for 5 of the institutions further demonstrates the willingness to work together to achieve efficiency and cost savings. In a state with poor support of higher education, it is essential that the major public universities (CU-D, CU-B and CSU) collaborate and share core facilities and other resources to be successful, and this is certainly the case in Colorado. Leadership at each of the 6 hospitals is also committed to the mission of the CCTSI and the CU Health Profession Schools in order to achieve their own missions. Thus, the VCHA of CU-D meets regularly with hospital Presidents and CEOs of all the partner institutions, further ensuring open communication channels for challenges that may arise. It also should be emphasized that faculty at CSU, CU-B and CU-D collaborate on literally hundreds of projects each year across institutions, co-mentor graduate students, publish together and are co-investigators on grants, demonstrating the collegial relationships between the academic institutions themselves. Finally, the many rich educational programs of the CCTSI are available to trainees and faculty at all of the partners. Thus the national reputation of our institution as a highly collaborative environment in which to work permeates through the CCTSI programs and partnerships.

Contributions of CCTSI: Each university and academic hospital will contribute to the CCTSI scientific collaborations, faculty and mentors for training programs, faculty for administrative CCTSI positions, patients for clinical studies and trials and clinical research space (hospitals), core facilities, and will include active Members of the CCTSI and contribute to clinical and translational research and training. CSU has unique attributes in veterinary sciences including Natural Animal Models of human disease, CU-B has outstanding strengths in biochemistry and integrative physiology, and the AMC is the home to all health profession schools in the state (see **Facilities and Other Resources**). Our medical and nursing schools rotate students and residents through all of the participating hospitals and their physicians and researchers are faculty members of CU-D. Thus, there is a bi-directional give-and-take that has functioned exceptionally well for decades

Decision-making and input: The CCTSI EC will include a lead representative from each partner University who will participate in decision-making and strategy. There will be researchers from each hospital on our Core Program Steering Committees and other committees (e.g., Pilot Grant review panels). Dr. Sokol will conduct town hall meetings each 1-2 years at each participating partner to provide information and receive input from interested faculty. In addition, to effective integration across the partner institutions, representation on the CCTSI Advisory Council (which meets biannually) includes high ranking leadership from each partner hospital and university campus, as well as the health profession school Deans.

Communication: Dr. Sokol will meet regularly with research leaders at each hospital and university, he will be a member of numerous institutional oversight committees, there is participation by conference call of leaders from CSU and CU-B for all EC meetings, and the CCTSI had a quarterly newsletter sent to all 4,25 Members. In addition, CCTSI has a Communications Director, Wendy Meyer, who provides announcements, arranges town hall meetings, provides outreach and marketing of CCTSI programs to all partner institutions and their constituents, and is part of the national CTSA Consortium communication working group.

B.3. Leadership of CCTSI Programs. (*Please see Biosketches and Budget Justification for academic and professional achievements of each individual listed below)*

Ronald J. Sokol, MD*,* the PI and Director of the CCTSI (responsibilities are described in B.1) since its inception in 2008, will continue in these roles in the current proposal. Dr. Sokol will have the responsibility and authority for all aspects of the implementation and function of the CCTSI and will have daily involvement with the activities of the CCTSI. He will oversee the 8 Associate Directors, the Executive Committee and the Administrative Core, as well as all operations. Qualifications for this position include Dr. Sokol's scientific, leadership, administrative and organizational experience as prior Program Director of the Pediatric GCRC for 10 years before becoming Director/PI of the CCTSI in 2008. He has a long investigative career in childhood liver disease, and has been PI on NIH funded basic, clinical and translational research grants for 30 years and holds a T32 training grant in pediatric gastroenterology. Dr. Sokol has chaired a national 15-site NIDDK-funded pediatric liver disease research network (ChiLDReN) for the past 15 years, providing him collaborative leadership experience across a consortium. Dr. Sokol will devote 4.5 months effort to the PI/Director position.

Tim Lockie, MS, MBA, Administrative Director and Chief Financial Officer (responsibilities are described in B.1), has functioned in this position since 2008 following the same position in the Adult GCRC for 4 years. Mr. Lockie has a scientific background (MS in Medical Genetics) and finance background (MBA) as well as years of operational, grants management, clinical research infrastructure development, and fiscal management experience at CU-D. Mr. Lockie has forged strong relationships with senior administrative and finance leaders

of CU-D, each of the schools, and all of the CCTSI affiliated hospitals and institutions. His extensive administrative and financial experience provide him with the abilities to undertake the role of Administrative Director and CFO for this large program. Mr. Lockie will devote 12 months effort to this position.

The following **8 CCTSI Associate Directors** will be responsible for directing the operations and functions, implementation, and oversight of one of the Core Programs (**see Fig. 1**), manage its budget, report to the PI/Director, and sit on the CCTSI Executive Committee:

Alison Lakin, RN, LLB, LLM, PhD, CCTSI Director for Research Methods, has extensive experience in research regulatory science, and has been the CU-D Associate Vice Chancellor for Regulatory Compliance since 2011. Dr. Lakin was Director of the Institutional Review Board (COMIRB) from 2005-2011, as well as the director of the CCTSI Regulatory Knowledge and Support Core 2011. She is director of CRAO, with goals to increase the efficiency and effectiveness of the regulatory approval process, contracting and research management and improve the quality of research. Dr. Lakin will sit on the CCTSI Executive Committee. Dr. Lakin will develop policies and procedures, oversee the budget, activities and personnel of this program.

Wendy M Kohrt, PhD, CCTSI Director for Hub Research Capacity, PCI and ISP, is a tenured Professor of Medicine in the Division of Geriatric Medicine at CU-D. Dr. Kohrt is an NIH supported clinical investigator, continuously funded for more than 25 years, whose research focuses on lifestyle and pharmacologic interventions to mitigate metabolic and functional declines with advancing age. She is the Director of the Energy Balance Core Laboratory for the NIH-sponsored Nutrition and Obesity Research Center, and the Chair of the CCTSI SARC and PCI Oversight Committee for the past 5 years. She will oversee these programs and sit on the CCTSI Executive Committee and devote 20% effort (2.4 months) to this position.

Lisa Cicutto, RN, MSc, ACNP (cert), PhD**,** Director for Translational Workforce Development, PI of TL1 NRSA Training Core and Associate Director CCTSI KL2 Career Development, is an accomplished researcher in lung health and has sustained uninterrupted extramural funding since 1998. Dr. Cicutto will be responsible for directing the overall activities of the TWD programs and participate on national Workforce Development Task Force. She will serve as the PI for the CCTSI TL1 Training Core (NRSA). Additionally, she will maintain her role as Director of the Clinical Science Graduate program which she has done for past 8 years. Dr. Cicutto is a faculty in Colorado School of Public Health and the College of Nursing and at National Jewish Health. Dr. Cicutto will devote 7.2 months effort.

Donald Nease Jr**.,** MD, MPH, Director for Community Engagement and Research, is Associate Professor and Vice Chair for Research in the Department of Family Medicine at CU SOM. Dr. Nease also directs the Colorado SNOCAP (State Networks of Collaborating Ambulatory Practices and Partners) practice-based research network collaborative which is also based at the University of Colorado. Dr. Nease has over 20 years of experience in practice and community based research in topics that include mental health care, cancer prevention and control and health information technology. Dr. Nease will direct the Community Engagement and Research program, organizing the innovative Partnership of Academicians and Communities for Translation (PACT) and ensuring community engagement and public trust in our research and training endeavors. He will sit on the Executive Committee and report to Dr. Sokol and devote 2.25 months effort.

Michael Kahn, MD, PhD, CCTSI Director for the Translational Informatics Program, currently holds the same position and has done an outstanding job the past 9 ½ years establishing the CCTSI informatics program. Professor of Pediatrics, he developed translational informatics infrastructure and services across the CCTSI campuses and affiliated hospitals and created and directs the Health Data Compass Data Warehouse at CU-D. He is a National Library of Medicine trained Informaticist, past co-Chair of the CTSA Consortium Key Function Committee on Informatics, and an expert in data security, data sharing, data standards & ontologies and clinical trials data acquisition. He will sit on the Executive Committee and devote 2.25 months effort to this position.

Elaine Morrato, DrPH, MPH, CCTSI Director of Innovation Ecosystem and the Dissemination Core, is a tenured Associate Professor and Interim Dean in the Colorado School of Public Health. Dr. Morrato is also a senior dissemination and implementation scientist at the Adult & Child Consortium for Health Outcomes Research and Delivery Science (ACCORDS) and former Collaborative Scientific Lead for an AHRQ Center for Research. Her research focuses on accelerating the translation of medical innovation and drug warnings into clinical practice. Dr. Morrato's 15-year tenure in Procter & Gamble's healthcare division launching new drugs and indications informs her implementation research and practice. Dr. Morrato is Site-PI and *Dissemination Core Director* for the Accrual to Clinical Trial (ACT) program funded by NCATS. She is also Site-PI for the Innovation-Corps (I-Corps™) program from NCATS. She will devote 1.8 months effort to these positions.

William W. Hay, Jr. MD, Director of ELEP, reporting to the CCTSI Exec. Committee and Dr. Sokol. He has directed the Perinatal CTRC program since shortly after its inception in 1970, and developed and directed the CCTSI CMH Program during its first two cycles. He also chairs the *ELEP Planning and Oversight Committee*,

with representation from across the CU-AMC and CCTSI from the Perinatal CTRC, Pediatrics, ObGyn, Medicine, Psychiatry, Pharmacy and Pharmaceutical Sciences, Dentistry, Nursing, School of Public Health, Native American affairs, and community partners. Dr. Hay is a voting member of the CCTSI Executive Committee. He will devote 0.9 Cal. Months effort.

Thomas Campbell, MD, Director of Translational Endeavors, Dr. Campbell is Professor of Medicine, Division of Infectious Disease and the Clinical Research Site Leader for the AIDS Clinical Trials Group at CU-D. Dr. Campbell has conducted clinical and basic research at the AMC for 27 years. He also serves as the Medical Director of the Clinical Translational Research Center at the UCH. In his role as Director of Translational Endeavors he is responsible for the development of the annual RFA's for each pilot grant program, oversight of the application receipt and review processes, assigning applications to reviewers, overseeing the review process and the prioritization of the selection of awardees. He will also track progress of the awardees and ensure compliance with the NCATS Common Metric. He will devote 0.9 months effort

B.4. Leadership Succession Plan: It is essential that the Program Director and Associate Directors undergo a rigorous annual evaluation with input from stakeholders, and that replacement be considered if performance does not meet expectations. The Director will undergo an annual performance review by the VCR and VCHA based on 1) an annual self-review, 2) information gathered by the VCR and VCHA, and 3) a written evaluation by the CCTSI EAC. The Program Director will evaluate performance of the Associate Directors, using objectives and specific criteria. Replacement of the Director or any Associate Director will be considered if they have not capably carried out the job responsibilities, if they are unable to perform all of their duties because of other responsibilities, or if they leave the institution or resign from their position. The VCR and VCHA will make the final decision on replacing the Director and the Director will decide on the Associate Directors. If replacement of the Director is required, the VCR and VCHA will assign an interim Director from the EC. Many members of the EC are now familiar with the workings of the CCTSI to be able to step into that role. The VCR will be the signatory for the Program Director in his/her absence. The Search Committee for a new Director will be chaired by the VCR and VCHA, and including Deans of the 6 health science schools (or their designee), CEOs (or their designee) from the 6 affiliated Hospitals, a high ranking representative from the CU-B, CSU and Downtown Denver CU-D campuses, and 5 faculty involved in translational research. The Search Committee will forward several ranked names to the VCR and VCHA for final approval. For replacement of an Associate Director, the Director will consider replacements after consulting with the other Associate Directors, the IAC/CTRAC, and the Deans of the 6 health science schools, with final sign-off by the VCR and VCHA.

B.5. Active Participation in the National CTSA Consortium and Steering Committee.

The CCTSI is fully committed to remain very active in the National CTSA Consortium, to cooperatively address impediments to research and science, to work towards adopting and implementing agreed-on best practices and standards and Common Metrics to advance clinical and translation research and training. We will participate in person in the 2 annual PD/PI meetings and participate on monthly PD/PI conference calls. We are committed to each of the national Strategic Goals and have and will maintain representatives on each of the Domain Task Forces, who will communicate back to the EC and vice versa. Dr. Sokol is willing to serve on the **Steering Committee (SC)** of the consortium, will volunteer for this position in year 2-3 of the new grant cycle, and will commit to attend all SC conference calls, face to face meetings, email communications, and other activities as needed. As an SC member he will then communicate the deliberations of the SC with a Pod of 6 CTSA Hubs through a monthly conference call, and become the communicator of the Pod concerns or suggestions back to the SC on a regular basis. Furthermore, Dr. Sokol would be willing to participate in additional conference calls, webinars, email communications or F2F meetings held between the SC, Pods, or Hubs. We are strongly committed to the concept of the **Trial Innovation Network**, a national networked CTSA infrastructure in which clinical and translational studies and clinical trials can be expedited through more rapid contracting, streamlined and cooperative IRB approval models, and provision of efficient and compliant resources and services. Furthermore, we are committed to adopting software developed by Consortium members that will increase efficiency and apply standards for better data sharing. Each of our academic institutions and hospital affiliates have pledged to work towards adopting and implementing the agreed on policies, procedures, best practices, and other measures established by the National CTSA Consortium and the NIH, including the data and software sharing plans described in this application (*see* ***Letters of Support***).

B.6. Collaborative Leadership and Communication. The CCTSI leadership and EC, which includes leaders across CCTSI programs and institutions sitting at the table, have had an outstanding collaborative working relationship for the past 9 years with strong communication and engagement of our partner institutions. For decisions resting with the EC, we anticipate that a collegial consensus will continue to be the mode of decision

making. If critical issues arise that cannot be decided through consensus, the Program Director/PI will discuss them with VCR and VCHA and come to a final decision. The CCTSI Advisory Council will be an additional venue for open discussion of issues that cut across institutional boundaries, with high level institutional representation present for meetings. We have several principles that we will enact: CCTSI resources will need to be prioritized for NIH-funded or other federally funded investigators, trainees and investigator-initiated research projects. After funding source is considered, allocation to Member investigators and trainees will be based on merit and need and not on their location or academic affiliation. The decision making processes for allocation will be transparent and fair. If conflicts arise between the major CCTSI institutions that cannot be resolved at the PI/Director level, CU-D highest leadership (Chancellor, VCR and VCHA) will become involved. We do not anticipate such situations to arise given the collegial, collaborative and respectful relationship between CCTSI stakeholders.

At times **resource allocation** may require difficult choices given our flat budget, but it will be handled in a fair and transparent manner. Data collected by Associate Directors, study tracking systems and Evaluation Core (based on objectives & metrics for each Core/Program) will be submitted to the Administrative Core in the fourth quarter of each year. Using these data as performance measures, the PD/PI and Admin. Director will determine appropriate budget and resources for each program for the upcoming year. Actions taken may include increased support for a component, re-allocation of resources to a more utilized component, instituting strategies to increase utilization, termination of a program or component director, etc. Factors under consideration for allocation of resources will include 1) the value of the Program/Core to the mission of the CCTSI, 2) utilization of the resources and the performance measurement for the prior year, 3) potential negative impacts if the function were to be scaled back or eliminated, 4) the proposed budget for the next year and 5) the availability of funds either from the NIH grant, program income or institutional support. The final decision on the distribution of resources and the budget will be made by the Director and will be shared with EC, the IAC and the EAC.

CHCO is participating in several **PEDSNet PCORNet** projects including projects in childhood IBD, cardiovascular disease and depression, with Michael Kahn, MD, PhD being one of the lead informaticists on these projects. Since Dr. Kahn sits on the CCTSI EC and directs our Informatics program, we have and will in the future incorporate PCORNet opportunities and collaborations into the CCTSI operations and information rolled out to our Members. The opportunity to use Health Data Compass (data warehouse) and PCORNet programming presents a unique opportunity for lifespan investigators.

Finally, **synergy between our UL1, TL1 and KL2 components** is built into our EC structure, with Lisa Cicutto, RN, PhD, who oversees our workforce development programs, our Clinical Science PhD and Masters programs, and the TL1 program, being an active member of the EC. We will also invite Cara Wilson, MD to EC meetings at least twice yearly, to update and engage the EC with results of the KL2 program. With all of the Core Program directors attending each 2 weeks our EC meetings, we have built the structure to ensure optimal communication and integration of our TL1 and KL2 programs with our UL1 objectives. Finally, our Communications Director and Evaluation Core work with our TL1 and KL2 directors, as well as UL1 Core programs, with the EC reviewing and discussing the evaluation of each of these programs annually.

2). EVALUATION AND CONTINUOUS IMPROVEMENT. *Specific Aim 2: Develop processes for Evaluation and Continuous Improvement that ensure responsive tracking of metrics, assessment and evaluation.*

A. SIGNIFICANCE

Efforts related to tracking, assessment and evaluation of the CCTSI are being conducted by our Evaluation Core based at The Evaluation Center, CU-D Downtown Denver Campus, in coordination with our Quality and Process Improvement Program (QPIP) in the Administrative Core. The Evaluation team is comprised of Ph.D.-credentialed evaluation professionals (Kathryn Nearing PhD and Jeffrey Proctor, PhD) who, with senior-level staff support, collectively bring more than 6 decades of experience with conducting large-scale evaluations for NIH, NSF, CDC and the U.S. Department of Education. The team includes evaluators with specialized quantitative and qualitative expertise who have applied their skills to develop rigorous quasi-experimental designs, engage in policy analysis, and support broad-based organizational change and capacity-building initiatives. A rigorous, external tracking, assessment and evaluation program, coupled with a formal, internal quality and process improvement program, will ensure the most efficient, cost-effective, and innovative use of resources, while protecting the safety of study participants. As the external evaluator, they will be chiefly involved in the next grant cycle in examining and documenting the impact of the CCTSI through **3 aims**: **Aim 1**. **ensuring continued alignment of evaluation and tracking with current and anticipated Common Metrics; Aim 2. demonstrating the quality and effectiveness of innovative programs and approaches through rigorous program evaluation; and Aim 3. supporting dissemination of CCTSI's model programs and implementation throughout the CTSA network through (a) the establishment of validated tools that can**

support fidelity of implementation, and (b) standardized evaluation of model programs developed locally. The results of the Evaluation Core's work will inform the Director/PI and Executive Committee on priorities for process improvement initiatives to be conducted by QPIP. *The evaluation of the KL2 and TL1 programs are outlined in Components I. and J. of the grant*. In this section, evaluation plans related to assessing CCTSI's local impact on CTR as well as collection of Common Metrics of the CTSA Consortium are described.

Needs Assessment: Evaluation Core administered comprehensive needs assessments in 2011, 2014 and 2016 to CCTSI members at all CCTSI-affiliated organizations, as well as all investigators and research support staff at the Anschutz Medical Campus. The purpose is to determine the resources/services that investigators consider essential and the extent to which these needs are effectively met. Results of the 2011 and 2014 needs assessments informed a number of new initiatives undertaken during the current grant cycle. The **CCTSI External Advisory Committee (EAC)** also reviews CCTSI progress annually, makes important recommendations, and submits an official report (see section B.5. below),

B. APPROACH

B.1. *Aim 1:* Evaluation Core will focus on continued involvement in national **Common Metrics** workgroups. Based on resident expertise, lead program evaluators (Nearing and Proctor) currently contribute to the following Common Metrics workgroups: Community engagement, Life course/lifespan, and Innovation. We will comply with the current and to be developed Common Metrics reporting requirements and report these, as well as local, priority metrics, to the electronic CTSA consortium **Impact Scorecard** of the **Results-based Accountability System** in accordance with required timelines. We will then convene key member meetings with individuals representing leadership and administration of each of the evaluated programs. During these meetings, we will discuss trends in the metric, important context needed to interpret each metric (story behind the curve), any action steps necessary for addressing the metric (turn the curve plan), and base these action steps in literature and best practices (what works). These data points will often surface questions which may be further explored through internal evaluation efforts. Finally, we will maintain strong partnerships with local owners of institutional data, such as the CU Office of Grants and Contracts, COMIRB, the Clinical Trials Management System (OnCore) and the Graduate School, to supplement primary source data collection, the goal being to ensure the accuracy and completeness of Common Metrics reported by the CCTSI. We will establish, when possible, informatics and electronic solutions to accurate real-time collection of Common Metrics data, interfacing with OnCore, COMIRB Epic, Health Data Compass or other local data sources. Leveraging primary and secondary data sources will give the CCTSI enhanced capacity to examine "the story behind the curve" and make necessary adjustments with enhanced agility.

B.2. *Aims 2 and 3:* will focus on the application of our local evaluation expertise to support **demonstration and dissemination**. Specifically in relation to Aim 2, quasi-experimental evaluation designs will be used to establish evidence regarding program impacts – evidence that can be used to determine whether a given program model/approach warrants scaling up for national dissemination. Aim 3 applies specifically to locally-developed programs that have a sufficient evidence base to justify national dissemination. Evaluation expertise will be applied to support fidelity of implementation as a prerequisite for examining reproducibility of program outcomes. For example, the Evaluation Core will develop rubrics that expert reviewers can use to objectively evaluate the degree to which a Translational Workforce Development program is being implemented with fidelity at a new site. The results can be used with new adopters to determine areas where more training and support may be needed to enhance fidelity. The evaluation team will also work with evaluators at newly-adopting sites to build sufficient capacity to implement a standardized evaluation plan in order to determine the extent to which program outcomes are reproducible and generalizable. This approach is described in detail in relation to CCTSI's Co-Mentor and LITeS programs (see Components D. Translational Endeavors (TWD) and I. KL2).

B.3. *Needs Assessment Surveys*. Over the 5 year proposed grant period, Evaluation Core will conduct needs assessments of investigators and trainees each 2-3 years and focus on trends emerging about the cost, level of utilization, and value of the resources/services for CTR research at our institutions. The Executive leadership and QPIP will utilize these data, as well as the financial reporting generated by the program income system, in annual data-informed decision making and resource allocation.

B.4. *Development of Local Indicators of Success and Metrics.* During the first year of the proposed grant cycle, Evaluation core will work closely with each CCTSI program and key function to develop logic models and associated immediate, intermediate and long-term outcomes. These logic models will inform the development of detailed evaluation matrices, organized by key evaluation questions and domains of interest, which will lead to development of local indicators of success, metrics and methods/data sources. A similar process will guide local evaluation activities over the next 5 years. **Study Life Cycle metrics**. Specific metrics have been developed for Protocol Tracking (see Quality and Efficiency below) which will be monitored at least annually by the PI and the

Executive Committee in coordination with the Evaluation Core. Implementation milestones and timelines will be developed and tracked for each program, as during the past 9 years.

B.5. *EXTERNAL ADVISORY COMMITTEE (EAC).* We have established an EAC which has been in place for the first 2 cycles of the CCTSI. EAC will meet annually at CU-D to provide an annual written review of CCTSI program progress, provide guidance to challenges that have arisen and make recommendations to PI/PD. For the new grant cycle, current members of EAC will be reappointed because of their excellent service over the past 5 years. Appointments are approved by VCR and VCHA under recommendation of PI and Executive Committee. The EAC will consist of 6 nationally renowned CTR scientists with individual expertise and extensive personal experience relevant to the CCTSI mission. **Members of the EAC will include**: 1) EAC Chair: Steven Dubinett, MD, PI of the UCLA CTSA and Assoc. Vice Chancellor of Research UCLA, a T1-T2 pulmonary scientist, 2) James Heubi, MD, PI of the Univ. of Cincinnati CTSA, a pediatric GI physician scientist, 3) Rex Chisolm, PhD, Assoc. VP for Research, Northwestern University, an accomplished informatics expert, 4) Joe Garcia, MD, former VP for Health Sciences, Univ. of Arizona, an outstanding T1-T2 pulmonary scientist, 5) Kevin Grumbach, MD, MPH, Chair of Family & Community Medicine, UCSF, a leader in community engagement & health, and 6) Doris Rubio, PhD, Director of Center for Research on Health Care, Univ. of Pittsburgh, an expert in biostatistics, education programs & evaluation. In the proposed grant cycle, we will add a Community Organization leader (TBN) from Colorado as the 7th EAC member. The EAC report will be reviewed by Dr. Sokol a) with VCR and VCHA for plans developed to address institutional issues, and b) with EC for operational issues.

The current EAC has been instrumental in **providing recommendations** which have spawned major changes and new initiatives. For example, the EAC identified that translational informatics lacked an academic home at CU-D. Upon these recommendations, Dr. Sokol and Informatics Director Dr. Michael Kahn led a major initiative at CU-D that culminated in 2012-3, with SOM Executive Committee approving a new Center for Biomedical Informatics at CU-D and a Division of Biomedical Informatics and Personalized Medicine in which academic appointments will be made. Kathleen Barnes, PhD from Johns Hopkins was subsequently recruited to direct these programs. The EAC also made the strong recommendation that CU-D needed to formalize data sharing and establish a research data warehouse among our partner institutions. In response, CU-D, UCH and CHCO funded a new data warehouse at CU-D (Health Data Compass – see Component B. Informatics) which is now fully functional and directed by Dr. Michael Kahn, CCTSI Informatics Director. The EAC also advised to expand quality & regulatory responsibilities beyond only those studies supported by CCTSI resources. CCTSI responded by a) making REDCap available across all campuses & hospitals for all studies, totaling over 2,500 projects, b) expanding RKS Core & CRAO to assist all translational investigators, and c) requiring SARC to perform scientific review for all clinical research studies of more than minimal risk across CU-D.

3). QUALITY AND EFFICIENCY. ***Promote a system-wide approach to ensure the highest Quality, Efficiency and Safety in the entire clinical study life cycle.***

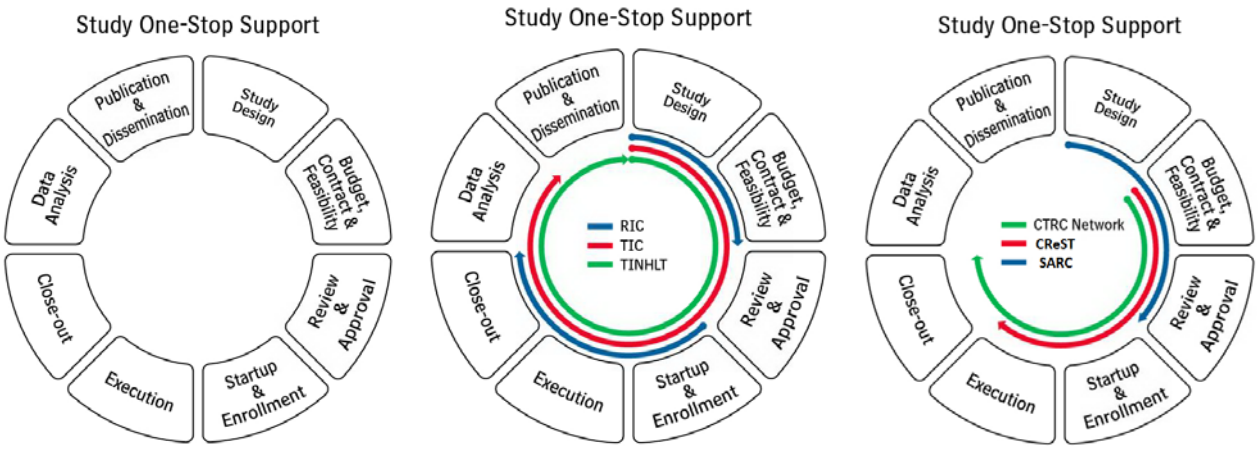
A. SIGNIFICANCE. A critical goal of the CCTSI is to ensure that research performed at CU-D and partner institutions is of the highest quality, that innovative team science is promoted, that we maximize efficiency in our operations and the conduct of clinical trials and that the safety of human research participants is of the highest priority. We will approach this goal by re-engineering and improving our Clinical Research Management through the following initiatives.

B. APPROACH.

B.1. Quality and Study Life Cycle. We will ensure high quality research through a variety of mechanisms, which form our **Study One-Stop Support** (**SOS**) concept. Through the coordinated efforts of CRAO, RKS, SARC, OGC, TIN and the UCH and CHCO hospital research committees, we will present the investigator with coordinated assistance for negotiating the complex processes inherent in the study life cycle (**Figure 4**). Our CCTSI Core programs will offer SOS assistance in specific ways to facilitate completion of the study lifespan from study design through close-out and dissemination. Some examples of how CCTSI programs collaborate to accomplish this are presented in **Figure 4,** and described below and in specific sections of this proposal.

Study design assistance will be provided directly through the **Research Incubator Studio (RIS)** program in which a content expert team is assembled to meet with an investigator to address questions related to design of a proposed study. Based on the Vanderbilt Studio Model, the RIS will bring together an interdisciplinary panel of 4-5 experts to assist an investigator or team with a specific research question, such as hypothesis generation, study design, research team building, grant review, implementation advice, or analysis interpretation. The goal is to offer multidisciplinary input and ensure high quality research at critical times in a research project trajectory. Jane Reusch, MD will continue to direct this program, which has received outstanding evaluations by those that have participated in the > 35 studios held over the past 3 years.

Figure 4. Study One-Stop Support (SOS)



To enhance quality throughout study life cycle, we will initiate **Study Jump-Start Consults** to provide *easy-accessible* comprehensive, integrated study design consultations at earliest stages of research development. (see Component E. Research Methods). Representatives from BERD, RKS, ethics, community, and informatics will team up with the investigator to outline a project plan, timeline, a project monitor and steps to be taken in parallel to ensure that high quality study is ready for start-up without delays. BERD will also offer **Design and Analysis Collaborations** for high priority science which will be determined by the following: 1) CTSA TIN referral, 2) high need for design and analysis collaboration (e.g., new data sources, no established design/analysis approach), and 3) large design and analysis component in proposed project (e.g., high return on investment). Both of these new initiatives will be tracked and evaluated by our Evaluation Core. Biostatistical Consultation (**BERD Core**) is also available to assist investigators at all levels of sophistication with study design. The Responsible Conduct of Research seminar series and Biostatical Seminar series include sessions on study design techniques and adaptation. Finally, formal coursework on study design is available in the Clinical Sciences Graduate Program.

CCTSI scientific review of proposed study protocols will also ensure only those with high quality proceed to approval. Our CTRC Scientific Advisory and Review Committee (**SARC**) will provide scientific review of all patient-oriented, non-peer reviewed research protocols prior to submission for IRB review, campus-wide, advising PIs of resources available if they need assistance to improve study quality. Our single Web Portal for submission of all SARC, IRB and hospital research committee documents has and will continue to greatly enhance speed, simplicity and accuracy of study proposal submissions. Our RKS Core and the CRAO office (and TIN Hub Liaison Team for TIN studies) will assist researchers to perform a newly required feasibility assessment and a budget review, using tools developed by our Informatics Core, both locally and for multi-site studies (see Components E. Research Methods and G. Network Capacity). For study execution, the CCTSI will provide a highly trained and certified research staff at our 5 state-of-the-art clinical research facilities (CTRCs), ensuring regulatory compliance, accurate data and specimen collection, and efficiency in the conduct of studies and trials. Our new CReST program will supply study coordinators on a fee-for-service basis. Recruitment assistance will be supplied by our CRAO recruitment facilitator, TIN recruitment liaison, and the RICs. The Informatics Core will also assist with recruitment using tools such as i2b2 and TriNetix to search Health Data Compass (data warehouse) for eligible subjects, as well as to provide study alerts for providers and patients. Each participating hospital has a Research Pharmacy with the expertise, equipment and oversight to manage study drugs according to FDA and other regulations.

B.2. Study Monitoring and Failing/Troubled Studies. However robust the feasibility modeling, there will be studies that encounter problems with recruitment and retention or other operational issues. Study Monitoring Committees (SMC) will review studies conducted at all 5 CTRCs. To further facilitate consistency across the CTRCs, a recruitment plan will be developed at beginning of each study by the Research Specialist in CRAO and the PI which will establish the parameters for successful, acceptable, and failing studies. The SMC will be charged with reviewing recruitment metrics for each CTRC study annually based on data entered into OnCore. If a study is identified as "failing" by the SMC, an improvement plan will constructively be developed with the PI. If a credible plan is not formulated or if it fails, a report of the issues will be sent to COMIRB to consider with the next continuing review. COMIRB has the authority to close failing studies. Once this process has been effectively implemented for CTRC protocols, it will be expanded to include all investigator-initiated and multi-site protocols at all partner institutions under the authority of COMIRB. Metrics will include the number and percent of studies that are closed by COMIRB and reported to PI and EC.

B.3. QPIP. To further maximize our efficiency and effectiveness, we will continue our very successful CCTSI Quality and Process Improvement Program (QPIP) that provides system-wide recommendations for change. Recognizing that increased quality, decreased waste, and efficient and transparent processes are hallmarks of contemporary translational research organizations, the CCTSI transformed its organizational structure in 2012 by incorporating QPIP. QPIP will, through direct interaction with CCTSI management, work to: 1) Identify and remove obstacles to efficiency and process improvement in priority areas, 2) Form clearly identified and empowered process improvement teams, 3) Link with Evaluation Core to ensure efforts are complementary rather than redundant, and 4) Integrate quality and process improvement into CCTSI governance and decision-making structures.

QPIP is made up of seasoned quality and LEAN-trained process improvement medical professionals, directed by Bethany Kwan, PhD. The QPIP team will apply its expertise to improve processes that are considered critical to a successful and efficient CTR enterprise. QPIP assessments have already led to re-engineering of the CCTSI BERD core, our research participant scheduling process, our personnel deployment in our CTRCs and other operational improvements. By end of Yr 1, QPIP will carry out a 10-step process for 3 priority areas to be identified. These efforts will culminate in a formal report to the CCTSI PI/Director and the EC on the findings, process revision recommendations, and lessons learned for each of the 3 priority areas. QPIP will ask the EC to take formal action to adopt revised processes and to fix responsibility/accountability for their maintenance (including the establishment of ongoing metrics for evaluation) and future revision/ improvement. Additionally, QPIP will establish a CCTSI Process Improvement Toolkit for use by the QPIP team and CCTSI process owners to initiate and complete their own process improvement activities with a minimum of facilitated assistance from QPIP.

C. DISSEMINATION*: Specific Aim 4: Disseminate successful solutions to translational barriers locally and throughout the CTSA Consortium*.

C.1. SIGNIFICANCE: An NIH-supported environmental scan of national D/Implementation training leaders reported that current programs face high demand and sustainability challenges, specifically in implementation practice. Our D/I Core will aim to address this critical workforce and translational gap through three aims.

C.2. APPROACH:

Aim 1. Support and facilitate a learning community and serve as a conduit for active local dissemination and integration of D/Implementation educational resources from NIH and other national organization. We will disseminate national standards and D/I best practices and trainings to CCTSI members and curate available NIH, AHRQ, and PCORI resources on our website. The CCTSI D/I unit will collaborate with the ACCORDS D/I program to create and promote seminar series, workshops, and intensive trainings on D/I methods and application, and develop new e-Books and graduate courses.

Aim 2. Catalyze and centrally support the CCTSI research community in the use of D/I research and methods, to achieve increased efficiency and economies of scale. We will continue to focus CCTSI D/I research consultations on major CU AMC center initiatives and training programs to augment ACCORDS's consultations with individual clinical investigators. This initiative will build and foster a sustainable and diverse research workforce with competencies to study delivery and implementation strategies for proven effective preventive and treatment interventions in real world practice.

Aim 3. Catalyze and centrally support the active bi-directional dissemination and implementation of (a) CTSA innovation inward into our local CCTSI ecosystem ("adoption" strategies) and (b) CCTSI innovation outward to the CTSA network ("scale-up" strategies). We will use Diffusion of Innovation Theory and develop local strategies to receive and implement/adopt trial innovations from the TIN. We will collaborate with the Directors of the respective CCTSI programs (RKS, Community Engagement, BERD, TWD, etc.) to design dissemination and evaluation strategies for spreading our local innovations across the CTSA consortium. We plan to build upon our CRISPeBook series to utilize this interactive web-based tool as our digital platform for broadly disseminating CCTSI innovation and tracking usage metrics. All activities of this Core will be tracked and evaluated by our Evaluation Core.

COMPONENT B: INFORMATICS

PROJECT SUMMARY/ABSTRACT

A vibrant translational informatics ecosystem requires technical and organizational engagement across the research data lifecycle (data collection, storage, analytics, sharing, and reuse). Investigators face challenges rapidly accessing integrated data sets in secure HIPAA-compliant analytic environments with support for data annotation, reproducible analytics, and open access archiving and sharing. With social media, mobile apps, and wearable devices, consumers are an additional collaborating partner. Cloud-based architectures offer new opportunities to rapidly configure and deploy informatics technologies and analytic tools in a secure scalable environment that "plays well" with external data partners, other CTSA Hubs, and the new CTSA Trial Innovation Network. A new challenge is enabling the seamless movement of data between clinical, personal, and research environments to support point-of-contact/personalized patient recruitment, real-time trial tracking, patient-reported outcomes, and continuous safety monitoring. True data liquidity requires integrating informatics tools at the point of clinical care or patient interaction, including social media and eHealth environments, requiring new relationships with institutional Health Information Technology (IT) operational partners, community-based collaborators, and innovative Internet/social media/mobile-savvy companies. To date, the **CCTSI Informatics Pillar Program** has fostered regulatory compliance and good data practices by enabling investigators to follow best-practices via no-cost access to secure user-friendly data management services. Our current objectives focus on linkages and workflows across operational, scientific (biological, clinical, population), patient/family, and consumer data owners to maximize data liquidity from any source to any place at any time while maintaining robust security, compliance, and confidentiality controls. We will achieve these goals through the following Specific Aims: **Aim 1:** We will link and harmonize administrative, biological, clinical, and public health data using our existing NIST 800-53 compliant secure research data warehouse data integration pipelines to create rich longitudinal data assets specifically to support broad-scale translational research. **Aim 2:** We will implement new infrastructure that supports data sharing and reproducible research. **Aim 3:** We will integrate the research data lifecycle into clinical-care practice and in patient-centered venues. **Aim 4:** We will expand our online educational resources to highlight next-generation research data infrastructures, data standards and annotation, reproducible research and data sharing best-practices. Eliminating barriers that separate clinical research and clinical care systems is necessary to "close the loop" with seamless participant notification and recruitment, trial enrollment, efficient trial execution, and rapid dissemination of new translational discoveries, all within a data secure and compliant environment. In collaboration with the new Trial Innovation Network, the Informatics Program Aims are built around these objectives coupled with providing investigator education and support for these new technologies.

COMPONENT B: INFORMATICS

SPECIFIC AIMS

The volume and diversity of electronic data sources has exploded, opening new opportunities to address previously unanswerable or unaffordable translational questions. Innovative informatics infrastructures that harmonize and analyze observations across many stages of translational research (biological, clinical, population) require new informatics methods beyond isolated research-only data systems. Evolving data annotation and reproducible research methods may increase return on investment. Rapid trial feasibility, cohort identification, and recruitment can increase the speed and success of new clinical trial designs. The CCTSI Informatics Program collaborates with local, regional, and national informatics activities to enrich investigator access to translational data. The Program supports key data models (i2b2, OMOP, VDW, PCORnet) and data sharing technologies (SHRINE, PopMedNet). Significant institutional investments include an integrated cloud-based research data warehouse (Health Data Compass, HDC) and a 750-CPU/4PB high-performance computing cluster. We provide informatics expertise to investigators in data integration, terminology harmonization, record linkage, common data models, multi-institutional data governance, and data quality assessment. We share informatics resources and partner with the new Colorado Center for Personalized Medicine to support large-scale bioinformatics consulting and bioinformatics computational services.

Despite strong existing informatics capabilities, investigators still face challenges rapidly accessing integrated data sets in secure HIPAA-compliant analytic environments with support for data annotation, reproducible analytics, and open access archiving and sharing. Our innovative cloud-based architecture offers new opportunities to rapidly configure and deploy informatics technologies and analytic tools in a secure scalable environment that "plays well" with external data partners, other CTSA Hubs, and the new CTSA Trial Innovation Network. A new challenge is enabling the seamless movement of data between clinical, personal, and research environments to support point-of-contact/personalized patient recruitment, real-time trial tracking, patient-reported outcomes, and continuous safety monitoring. True data liquidity requires integrating informatics tools at the point of clinical care or patient interaction, including social media and eHealth environments, requiring new relationships with institutional Health Information Technology (IT) operational partners, community-based collaborators, and innovative Internet/social media/mobile-savvy companies. The following **Specific Aims (SA)** achieve these goals by implementing new tools, creating new capabiities, and providing access to just-in-time training for data creation, integration, point of care use, data sharing and reuse:

Aim 1: We will link and harmonize administrative, biological, clinical, and public health data using our existing NIST 800-53 compliant secure research data wareshouse data integration pipelines to create rich longitudinal data assets specifically to support broad-scale translational research. We will leverage our extensive local technical experience with all major common data models and data standards.

Aim 2: We will implement new infrastructure that supports data sharing and reproducible research. We will implement tools that support data standards, annotation, reproducible analytics, and data-sharing best practices. We will partner with existing Open Science / Reproducible Research activities to ensure our efforts align with national approaches.

Aim 3: We will integrate the research data lifecycle into clinical-care practice and in patient-centered venues. We will partner with institutional IT leadership, CCTSI Community Engagement community leads, external health IT innovators on eHealth and social media tools to enable culturally-sensitive real-time patient recruitment alerts, point-of-care study-specific data capture, eHealth-based patient-reported outcomes and adverse events, and continuous safety monitoring rules at every potential point-of-contact.

Aim 4: Expand our online educational resources to highlight next-generation research data infrastructures, data standards and annotation, reproducible research and data sharing best-practices. We will develop an interactive dialog system that creates investigator-specific informatics and research data management educational plans based on unique data needs of their studies that will include links to relevant on-line resources created by the CCTSI and other CTSA Hubs.

Common Abbreviations used in this Component

ACT	Accrual to Clinical Trials	DMP	Data management planning tool	OMOP	Observational Medical Outcomes Partnership
CHORDs	Colorado Health Outcomes Research Data Service	FAIR	Findable, Accessible, Interoperable, Reusable	OHDSI	Observational Health Data Sciences and Informatics
CD2H	CTSA Program Data to Health	GCP	Google Cloud Platform	PMN	PopMedNet
CSU	Colorado State University	HMORN	HMO Research Network	SHRINE	Shared Health Research Informatics Network
U-HSL	University of Colorado Health Sciences Library	HSCRN	Health Systems Research Network	TICR	Translational Informatics Computational Resource

COMPONENT B: INFORMATICS

RESEARCH STRATEGY

A. SIGNIFICANCE

PAR-14-304 PHS 398 Research Plan (Informatics) states: "Biomedical informatics is a critical CTSA focus for enabling and advancing translational research, which is increasingly data intensive, and requires collaboration across many communities, including healthcare, research, and public health." With social media, mobile apps, and wearable devices, consumers are an additional collaborating partner. A vibrant translational informatics ecosystem requires technical and organizational engagement across the research data lifecycle (data collection, storage, analytics, sharing, and reuse) [1]. Integrating disparate data requires knowledge of and commitment to a wide range of data standards. To date, the CCTSI Informatics Pillar Program has fostered regulatory compliance and good data practices by enabling investigators to follow best-practices via no-cost access to secure user-friendly data management services. Our current objectives focus on linkages and workflows across operational, scientific (biological, clinical, population), patient/family, and consumer data owners to maximize data liquidity from any source to any place at any time while maintaining robust security, compliance, and confidentiality controls. Our future goals align with NIH commitments to data standards, sharing and reuse [2]. Balancing data accessibility with governance and transparency [1,3,4] will be critical challenges.

B. INNOVATION

In 2017, the Health Data Compass (HDC) Research Data Warehouse (see below) will complete its migration to Google Cloud Platform, the *first* integrated large-scale genomic, clinical, administrative, and population-based data warehouse implemented in this platform. During the next phase, new secure data integration pipelines for genomic, geographic, sensor/wearable devices, social media and other clinical and non-clinical external data sources such as the Colorado All-Payer Claims Database, will be combined with local health care and research data. Cloud platforms enable new approaches to data integration and secure access that are not possible with traditional on-premise resources. Collaborations with Google Brain will bring advanced analytics for data quality assessment, tools for large-scale terminology harmonization/standardization, natural language processing, non-demographic-based record linkage, and new approaches for deep clinical phenotyping for translational investigators. With infrastructure scalability and access to advanced analytics, the Google Cloud Platform is proving to be an exciting innovation-enabling architecture and public-private partnership.

C. PRELIMINARY DATA / INSTITUTIONAL ASSETS

Through local and national collaborations, the Translational Informatics Program has built expertise in a wide array of clinical research informatics (CRI) technologies for investigators. We adapt the newest innovations developed elsewhere into our local environment (Table 1 left). We also contribute our own innovations to CTSA Hubs and others (Table 1 right), illustrating bilateral sharing of specialized translational informatics expertise across the CTSA community. Since its creation in 2008, the CCTSI Informatics Program has provided a fully subsidized HIPAA-compliant REDCap data management service, including hands-on tutorials and consultations. Predefined REDCAP data collection forms with NIH and ONC/CMS compliant variable names and value sets provide reusable standards-based data collection across studies.

Table 1: (left) CTSA/CRI technologies leveraged from other CTSA hubs and (right) CRI technologies developed and shared by CCTSI Research Informatics with other CTSA hubs.

CCTSI Adoption/Implementation	
Applications / projects	NCATS ACT, PCORnet, CHORDS, SAFTINet, PEDSnet, pSCANNER
Research support	Colorado PROFILES, REDCap, i2b2, TrinetX
Sharing policies	NCATS ACT, PCORnet, CHORDS, COMIRB, CCTSI
Secure networking	SHRINE (i2b2), PopMedNet, TRIAD
Extracts / Data Marts	I2b2, OMOP, project-specific extracts
National Data Models	I2b2, HCSRN (HMORN) VDW, OMOP, PCORnet CDM
Institutional Data Repositories	Health Data Compass (AMC), EDW/RDW (CHCO, NJH, KPCO, DHHA)

CCTSI-created Innovation	
Workflow / Infrastructure	Pilot grant proposals submission, scoring, and review
	Training plans and course approvals
REDCap / Data Management	CheckMate: REDCap Excel macro checks for best-practices
	Data standards: Auto-generate annual COMIRB enrollment and SAE reports
	5x5 single-topic best practices videos
	Full REDCap training videos
	Integration of SAS-generated metrics and graphics
Data sharing networks	EPIC Clarity to OMOP ETL
	OMOP to PCORnet ETL
	EPIC Clarity to i2b2 ETL
Novel Methods	Clear-text record linkage
	Three-party encrypted record linkage

The informatics infrastructure has matured from stand-alone servers into a secure, fault-tolerant, VM farm with backup, disaster recovery capabilities, annual third-party security audits and penetration testing.

Table 2: Representative Informatics Program metrics (CY2016).

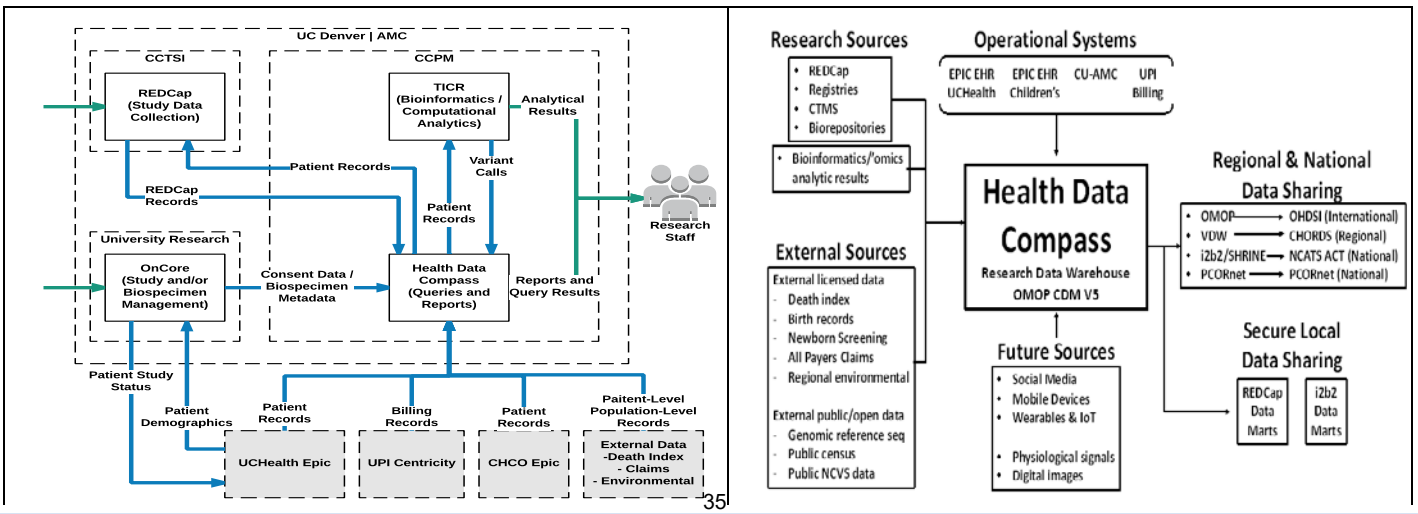
Infrastructure	
Systems	2 VMWare ESXi clusters, 62 virtual machines; SharePoint/Profiles/Harvest/Copia LIMs, SQL servers; Cold Fusion, FreezerWorsk, EPEvaluator, QuickBooks, file servers, virtual desktops, backup/DR service
Security	OIT NIST SP500-83 security controls
Web	CCTSI web site (sessions/page views): 48,000/161,000; Profiles: 126,000/247,000
Local	
REDCap	3191 active users / 5042 projects / 1214 tutorial attendees. Covers all CCTSI locations plus Denver VA.
CO Profiles	Four University of Colorado campuses, Colorado State University, affiliated investigators
Health Data Compass	OMOP / Google Cloud NIST SP500-83 security controls: Data sources: UCHealth, CHCO, CU-AMC, UPI, CDPHE, APCD, CORHIO
OnCore	AMC-wide CTMS + biorepository
TICR (Cluster)	750 CPU cores; 4TB memory; 4PB GPFS storage
Regional	
CHORDS	VDW/PopMedNet: Public health surveillance - 10 contributing institutions
National	
PCORI PEDSnet	OMOP + PCORnet CDM; centralized DCC
PCORI PORTAL	VDW + PCORnet CDM; distributed PopMedNet
NCATS ACT	CHCO: i2b2/SHRINE
PCORI Data Quality Methods	Harmonized DQ framework; standardized DQA data model; assessment of 1300 existing data quality checks

The Informatics Program managed explosive growth in demand by creating new efficiencies such as online training videos (redcapinfo.ucdenver.edu), innovative REDCap design tools (CheckMate [5]), and new functional capabilities with REDCap hooks and APIs. Our optimized processes allowed us to service almost 3,200 active users and over 5,000 projects (Table 2) in a regulatory-compliant and secure environment. Other infrastructure efforts focused on scalability, resiliency and security, including migrating the CCTSI VMWare ESXi/vSphere server farm into a NIST SP800-53 compliant data center. Table 2 provides metrics that highlight the extensive use of the Informatics Program services.

At the same time, the University of Colorado and affiliate partners have made substantial investments in their informatics infrastructures, significantly advancing the capabilities and impact of the CCTSI Informatics Program. In 2014, a $63M joint investment by the UC Health System, CHCO, the CU SOM and CU Medicine established **Colorado Center for Personalized Medicine** (CCPM: **see Overall Component).** CCPM hosts two notable trans-lational informatics resources (Figure 1a) -- the *Translational Informatics and Computation Resource* (TICR), a high-performance computing cluster for genomic sequencing and bioinformatics; and *Health Data Compass* (HDC), a multi-institutional research data warehouse. Similar data warehouses, data networks, and data governance activities have been deployed in CCTSI-affiliated institutions (Kaiser Permanente Colorado, Denver Health and National Jewish).

Responding to the strong recommendation of the CCTSI External Advisory Committee reports which highlighted the lack of a Big Data strategy at UC Denver, **Health Data Compass** (Figure 1b) was created and is now the clinical and translational research data hub for the AMC campus and the emerging Big Data analytics programs that combine genomic, molecular, clinical, administrative and public data sources using patient- and location-level record linkages to create integrated data resources. HDC is staffed by personnel with academic and technical experience in research design, clinical research, medical terminologies, and regulatory/Honest Broker requirements. HDC uses the OHDSI/OMOP Common Data Model (CDM) but also has technical hands-on experience with i2b2, HSCRN (HMORN) VDW, Sentinel, and PCORnet CDMs [6] and participates in PCORnet [7–10] and NCATS ACT. OMOP embeds over 40 standardized national and international terminologies, including

Figure 1: (a) Computational infrastructure for Colorado Center for Personalized Medicine (CCPM); (b) Data input and delivery options for Health Data Compass Research Data Warehouse within CCPM.



all CMS/ONC Meaningful Use terminologies. A full-time clinical terminology specialist (Registered Nurse with Masters in Health Informatics) provides terminology harmonization expertise to both HDC and CCTSI. Data access methods in HDC span self-service access via i2b2 and TriNetX to one-on-one data consultations. HDC is closely integrated with CCTSI functions: the CCTSI Informatics Program Director (Kahn) is also the Director of HDC. The CCTSI REDCap leader (Carlin) is co-located with and co-funded by HDC. HDC extracts are delivered as secure REDCap studies. HDC recently migrated from a traditional on-premise relational database to Google Cloud Platform (GCP), a significant private-public partnership and a *first-in-the-world* NIST 800-53 compliant health data warehouse deployment for GCP. With this transition, HDC has access to infinitely scalable storage and processing power, a rapidly growing set of large public genomic, biological, environmental, and public health data sets. New relationships with Google Brain, the Google data analytics team developing novel cloud-native computational capabilities that can be applied to the molecular, clinical, personal, and population-level health data on 5.5M patients.

A second notable multi-institutional translational informatics investment developed through the CCTSI is the **Colorado Health Observation Regional Data Service (CHORDS)**, a Denver metro regional data sharing network (https://goo.gl/7sBm1v). CHORDS provides data to public health stakeholders and clinical researchers using the HSCRN VDW CDM and the PopMedNet distributed query system [11,12] (Figure 2), borrowing technologies and governance from both HSCRN and PCORnet, where three CCTSI affiliate organizations are active participants. Geocoding, spatial population-level analytics, and map-based visualizations are widely used in the CHORDS data network. Funded by the Colorado Health Foundation, a community and stakeholder based governing board composed of technical and data partners, researchers and surveillance stakeholders oversee data stewardship, partnerships, and appropriate data use. All CCTSI affiliated institutions plus multiple Denver Metro safety net clinics, federally qualified health centers, and public health authorities participate in CHORDS. CHORDS has plans to continue expansion across all Front Range local public health authorities and to integrate population-level heath, socio-economic, community, and build data from the state public health databases.

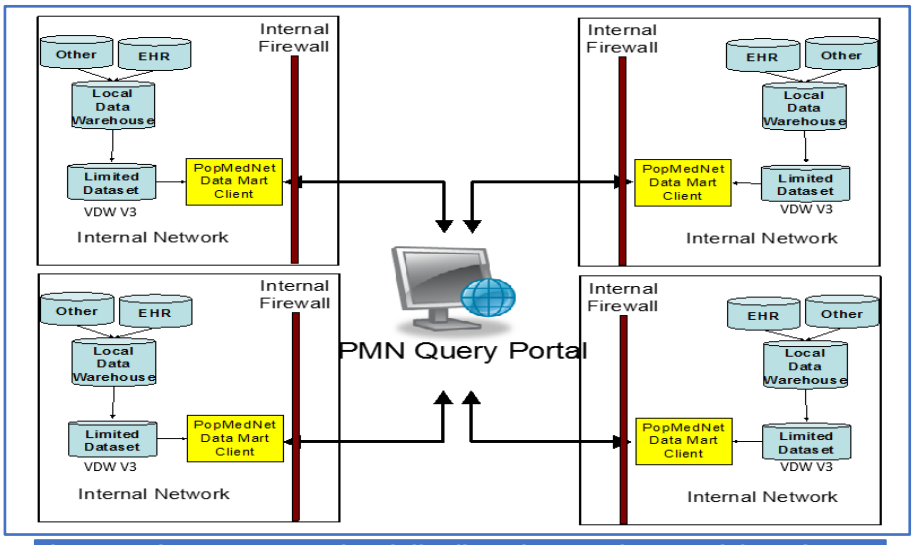


Figure 2: The CHORDS regional distributed research network based on VDW and PopMedNet.

D. APPROACH

In the new funding period, the CCTSI will focus on accelerating investigator access to integrated, linked data from clinical, administrative, local, regional, and national data partners plus mobile, sensor, and social networking sources. Translational use cases will include data-driven clinical research discovery, precision medicine, study cohort identification, rapid cohort validation and recruitment, and continuous safety monitoring. Eliminating barriers that separate clinical research and clinical care systems is necessary to "close the loop" with seamless participant notification and recruitment, trial enrollment, efficient trial execution, and rapid dissemination and implementation of new translational discoveries, all within a data secure and compliant environment. In collaboration with the new Trial Innovation Network, TICs, and RICs, our Aims for the Informatics Program are built around these objectives coupled with providing investigator education and support for these new technologies.

Aim 1: We will link and harmonize administrative, biological, clinical, and public health data using our existing NIST 800-53 compliant secure research data wareshouse data integration pipelines to create rich longitudinal data assets specifically to support broad-scale translational research. The CCSI Translational Informatics Program will leverage our extensive local technical experience with all major common data models and data standards used across CTSA Hubs to ensure data are annotated and sharable.

Acquiring, standardizing, and linking data from disparate data sources is an arduous task. Data sources may be internal systems, external partners, commercial vendors, government sources, or online portals including open-data repositories. A wide range of data processing challenges, collectively labeled "data wrangling" [13], security and access controls are often beyond the technical capabilities of investigators. For example, NIST 800-53

security compliance is a difficult, expensive goal that requires technological, administrative, and processes that far exceed the capabilities and resources of individual investigators. As translational research leverages the explosive diversity of health-related digital assets [14], new translational informatics infrastructures that accelerate data assimilation and analytics will become critical to advancing data-driven discoveries. Levering the HDC secure cloud-based infrastructure, our HIPAA-compliant REDCap eco-system, and unique translational informatics resources such as a full-time terminologist, the CCTSI Informatics Program will develop new processes and pipelines to facilitate data use while maintaining security and access controls.

Approach 1.1 (Yr. 1): With HDC and CHORDS as local and regional data partners, we will create data extraction specifications that are consistent with ONC/HL7 (FHIR) standards, NIH Common Data Elements, widely-used CDMs and data standards, such as the ACT i2b2 ontology [15,16], ensuring analytic data sets conform to data sharing standards at the time of creation.

Approach 1.2 (Yr. 1-5 continuous): We will expand pre-defined data dictionaries and training for standardized prospective REDCap data collection forms that are aligned with national data-sharing standards. We will submit forms to REDCap Shared Library (https://projectredcap.org/resources/library/) for use by the international REDCap Consortium. We will expand the CheckMate REDCap data dictionary "checker" to detect opportunities to modify REDCap forms to meet national data standards.

Approach 1.3 (Yr. 1-5 continuous): We will create REDCap data extraction routines for standardized forms developed in Approach 1.2 that export data sets consistent with one or more national common data models, such as OMOP, VDW, i2b2, or PCORnet.

Approach 1.4 (Yr. 2-5): Leveraging our national informatics leadership and convening roles in data quality assessment [17–23], we will construct a comprehensive suite of data quality assessment (DQA) profiling tools to detect missing or anomalous data elements [22], starting with the OMOP ACHILLES data quality profiling tool (https://www.ohdsi.org/analytic-tools/achilles-for-data-characterization). Define metadata standards for representation of DQA results in a formal structure that can be included as metadata submitted with published data sets, enabling investigators to evaluate if a data set is fit for their intended use.

Aim 2: We will implement new infrastructure that supports data sharing and reproducible research.

The NIH supports the FAIR (findable, accessible, interoperable, reusable) Guiding Principles for scientific data management and stewardship [24,25]. Robust, actionable data sharing plans backed by infrastructure tools for data annotation, storage, and discovery are necessary to achieve the FAIR principles. Tools for biomedical data annotation, curation, indexing, discovery, and sharing are starting to emerge. The BD2K-funded BioCaddie DataMed and the Center for Expanded Data Annotation and Retrieval (CEDAR) are two recent efforts for attaching metadata to be exposed to Internet search engines for data discovery [26]. The National Library of Medicine recognized the unique role of medical librarians in supporting data curation and archiving, providing training to a new generation of Medical Informationists [27–29]. Both the University of Colorado Health Sciences Library (CU-HSL) and the Colorado State University (CSU) Libraries have created Informationist positions. CU-HSL successfully received a NLM Medical Informationist grant award to pilot data curation and archiving projects.

In our current environment, CCTSI investigators do not have access to tools or processes to create discoverable data assets and reproducible analytic methods. The Informatics Program will implement new tools through collaboration with our libraries and will engage in national efforts to establish workable solutions:

Approach 2.1 (Yr. 1-3): In collaboration with Informationists at CU-HSL, we will implement processes to aid CCTSI investigators develop comprehensive data management and data sharing plans based on the standardized data models and terminologies. The University of Colorado subscribes to the Data Management Planning Tool (https://dmptool.org). We will develop DMP templates and support investigators that use these templates to reduce barriers to data annotation and data sharing. DMP templates will include sharing analytic methods in addition to standards-based data sets for reproducible analytics. As national data annotation standards emerge, we will ensure that our annotation tools incorporate these terminologies. To ensure early engagement of investigators with data standards and management plans, the Informatics Program will participate in the "Study Jump-Start Consults" organized by the BERD/RKS programs to assist investigators with design in the early phases of study development (**see Component E. Research Methods).**

Approach 2.2: (Yr. 3-5) In collaboration with Informationists at CU-HSL and CSU Libraries and established data discovery programs, we will install and support investigator-friendly data annotation tools that enable curation of data and analytic files, such as tools by CEDAR and BioCaddie. We will partner with the libraries to create online

training materials, which will be made available to other institutions. Anticipating significant socio-technical barriers to an additional task in data submission are likely to arise, we will initially target clinical coordinators and research associates, who are likely to have hands-on knowledge about study data elements.

Approach 2.3 (Yr. 3-5): We will assist investigators in depositing annotated data sets and analytic methods into public-facing, discoverable data repositories. The Colorado Alliance of Research Libraries has implemented a collaborative Digital Repository that is available to faculty across multiple campuses, including CU-AMC and CSU (https://www.coalliance.org/software/digital-repository). As national standards for data annotation and discovery services emerge and NIH Data Sharing Repositories are established, we will implement these metadata standards and annotation workflows so CCTSI investigators can contribute digital assets that meet the FAIR Principles. Since this is an evolving space, the Informatics Program will participate in national work groups such as BD2K (BioCaddie, CEDAR), NCATS, and DataCite, to ensure we incorporate new approaches as the CRI community creates implementable guidelines and best practices.

Aim 3: We will integrate the research data lifecycle into clinical-care practice and in patient-centered venues.

The traditional separation between clinical research, clinical care, and online media is being replaced by integrated processes for subject identification, outreach and recruitment, e-consenting, e-source data collection, automated study compliance, patient-reported outcomes, and safety monitoring [30–34]. The University of Colorado Hospital currently exchanges basic patient information via real-time messaging between EPIC's EHR and Forte Research's OnCore CTMS and key clinical variables with the AgileMD clinical decision support engine for complex predictive modeling and integrated order sets. With most patients seeking information on clinical trials thru online resources, the CCTSI partnered with TrialSpark (www.trialspark.com), a patient recruitment start-up that generates tailored trial recruitment messages to targeted social media sites to engage hard-to-recruit patient populations. We will expand linkages between operational systems, research systems and external systems, including social media-based communications platforms linked to clinical and research management systems, to create seamless data flows across care, home and personal settings.

Approach 3.1 (Yr. 1-5): With our hospital system IT and research operational leadership, we will establish joint governance and procedures to identify and prioritize real-time patient recruitment alerts within the EPIC EHR and patient portals. We will align this effort with existing EHR-clinical decision support governance and institutional consent and regulatory oversight to enable provider and patient-oriented trial eligibility alerts in normal clinical and patient portal workflows. We will follow best-practices to minimize alert fatigue and patient enrollment burden.[35–38]

Approach 3.2 (Yr. 1-2): We will create bidirectional EPIC and OnCore data exchange interfaces to enable exchange of **coded** clinical trial eligibility parameters and study-specific safety triggers, using implemented web services and FHIR interfaces. We will partner with operational HIT teams and commercial clinical decision support vendors, such as AgileMD, to modify existing web-services-based real-time patient identification methods that detect patients for guideline-based care to include trial eligibility triggers. We will expand existing oversight procedures for requesting, approving, and implementing clinical documentation changes that embed study-specific structured data capture into the operational workflows.

Approach 3.3 (Yr. 1-5): We will encourage investigators to incorporate innovative social media recruitment and eHealth data capture services via TrialSpark and other commercial partners by providing start-up funds for new studies to use these services (see **Component G. Network Capacity**). We will collect metrics to assess the impact of social media methods on recruitment times and eHealth applications on patient-entered data capture rates.

Approach 3.4 (Yr. 3-5): We will establish an EHR-Research Best Practices Collaborative Working Group with our affiliate institutions. This group will foster bilateral exchange of successful technical, governance, and evaluation practices for introducing research workflows into local EHR systems. Four of our CCTSI partner institutions have installed EPIC although each system supports institution-specific workflows and have different IT oversight structures. We will be active participants in CTSA-wide EHR-Clinical Research Integration activities supported by the CTSA Informatics Domain Task Force (iDTF) and CD2H.

Aim 4: Expand our online educational resources to highlight next-generation research data infrastructures, data standards and annotation, reproducible research and data sharing best-practices.

Like many CTSA hubs, CCTSI supports investigators across a wide geographic region. To facilitate anytime access to training materials, the Informatics Program created online video resources that are available via our local video library,YouTube and Vimeo (http://redcapinfo.ucdenver.edu). In response to the explosive rise and critical use of data sciences in translational research, including data "wrangling", record linkage, data sharing, and reproducible research methods, we must expand investigator training offerings to include these new data science/informatics tools. In addition, we have seen an increase in investigator requests for understanding clinical phenotyping methods, text mining, and the strengths and weaknesses of secondary use of EHR data.

Approach 4.1 (Yr. 1-5 continuous): We will create a translational informatics educational recommendation tool that links the informatics needs and features of a study to available educational modules that provide training/tips on relevant tools or methods. For example, an investigator that defines a study cohort using billing data will be directed to different training resources than an investigator performing a drug exposure study using inpatient EHR data. While optional, project-specific training modules should be more relevant to an investigator when taken while developing or starting a new study.

Approach 4.2 (Yr. 1-5 continuous): We will engage with our investigator community to determine data sciences topics deemed most relevant for new training materials. In light of the strong emphasis on data sharing, we will target development or acquisition of new online videos and new courses that focus on data standards, curation, annotation, and sharing plus reproducible research methods. We are aware of CCIA-funded N-Lighten federated platform for education resource sharing (https://goo.gl/OpE15B). We will both leverage materials made available on N-Lighten and contribute our materials if that platform expands in scope.

Approach 4.3 (Yr. 2-5 continuous): In addition to traditional "talking slides", we will assist faculty in creating hands-on exercises with sample code and data. We have created a de-identified inpatient and outpatient EMR data set that can be used to build sample scripts. In collaboration with HDC, the CCTSI will establish web-based analytic workspaces that contain databases and tools to support hands-on exercises. All didactic materials will be freely available to other CTSA Hubs and others at no cost via a public-facing GitHub site.

E. STRUCTURE, GOVERNANCE AND INTEGRATION

This Program will be directed by **Michael Kahn, MD, PhD,** Professor of Pediatrics and Director of Translational Informatics for the CCTSI since its inception in 2008 (see **Org. chart in Facilities & Other Resources**). Dr. Kahn is highly qualified to oversee the Informatics Program, with a 20+ year career in CRI, with a wide range of peer-review publications, most recently focused on research data warehouses, data quality, and common data models funded by NIH, AHRQ and PCORI. He is a Fellow of the American College of Medical Informatics, a college of elected fellows who have made significant and sustained contributions to the field of biomedical informatics. Table 3 illustrates the leadership structure of the four CCTSI Translational Informatics Program "pillars". Not shown are significant co-leadership or co-funding across additional campus activities, specifically HDC, TICR, OnCore, CHORDS, and PCORnet nor Informat-ics positions at affliated institutions.

Informatics Program Director: Michael Kahn MD, PhD	
Thomas Yaeger (Systems & Applications)	CCTSI Web site; .NET/SharePoint applications, Virtual server farm; Data security/Disaster recover.
Linda Carlin PhD (Data Management)	REDCap/Survey, API programming; Data management best practices/training. Data standards. Research data queries
Michael Kahn MD, PhD (Innovation & Collaborations)	Health Data Compass RDW; CHORDS regional network; PCORnet CDRN (PEDSnet, PORTAL)'; i2b2/SHRINE/ACT; TrinetX, External partnerships
Tzu Phang PhD (Education)	Bioinformatics tutorials; Monthly seminars

Table 3: Leadership structure for Informatics Program. Not shown are informatics leadership across institutional programs and within CCTSI affiliate organizations.

F. TIMELINE AND METRICS / EVALUATION

For our new activities, we have provided estimated time intervals for each Approach with their descriptions in D. Approach. Many activities are noted as "continuous" after initiation because we anticipate these services to be used by investigators once they are available and therefore will require on-going expansion and support by the Informatics Program. We will continue to capture our historical local service metrics (Table 2) which focus on investigator use of core informatics services. At the same time, the iDTF has initiated efforts to define global Common Metrics for informatics, which we will adopt, track and report through our Evaluation Core. For new services, we will define performance metrics that capture the utilization of each new service (e.g., use of linked data for study feasibility, open-access data sets in searchable repositories, social media-based recruitment) and add them to our standard service metrics in Table 2 and use them for continuous quality improvement.

COMPONENT B: INFORMATICS

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COMPONENT C: COMMUNITY AND COLLABORATION

PROJECT SUMMARY/ABSTRACT

Community Engagement (CE). The CCTSI places a high priority on engaging community members and other stakeholders in the full spectrum of clinical and translational research (CTR). The Community Engagement and Research (CE&R) Core will include a portfolio of innovative programs and relationships including a nationally recognized Pilot Grant Program. The Core has demonstrated the value and benefits of engaging patients and communities as active partners in research to address community priorities, design studies in a culturally-sensitive and participant-friendly structure, implement and disseminate findings into the community, and enhance public trust and participation in research. The CE&R Core will broaden the stakeholders with whom it engages and further integrate CE&R throughout the CCTSI, increase the bi-directional nature of its work, and integrate engagement work with that of its partners in team science at the University of Colorado (CU), Colorado State University (CSU), hospital partners, and the CTSA Consortium. To achieve these goals, the following Specific Aims are proposed: **Aim 1:** Expand the community stakeholders to include an array of healthcare organizations and payers to expand the potential for implementation and dissemination. **Aim 2**: Further infuse Community Engagement throughout the translational spectrum within all CCTSI programs and operations. **Aim 3**: Increase capacity for bi-directional engagement between researchers and community stakeholders to enhance the science of community engaged translational research.

***Collaboration and Multidisciplinary Team Science*.** The CCTSI has invested in the advancement of team science through incentives (e.g., leadership training in team science, team science pilot grant awards) that bring together investigators across different scientific disciplines and across different levels of the translational research spectrum to conduct innovative CTR. This Core will enhance and expand these programs by advancing the integration of community stakeholders in CTR research teams and by building a new Science of Team Science (SciTS) program. The SciTS program will be scaled up from activities first developed and evaluated at CSU. The overarching goals are to foster an environment that values team science research and to develop and evaluate evidence-based research team-building activities that enhance the success of research teams through the following Specific Aims: **Aim 4:** Catalyze translational collaboration and team science training and the engagement of community stakeholders with research teams. **Aim 5**: Implement a SciTS academic program to enhance the science and success of multidisciplinary research teams.

COMPONENT C: COMMUNITY AND COLLABORATION

SPECIFIC AIMS

Community Engagement (CE): CE, with meaningful involvement of community members in our research and training programs, has been a high priority throughout the 9-year lifespan of the CCTSI. We have demonstrated the value and benefits of engaging patients and communities as **active partners** in the full spectrum of clinical and translational research (**CTR**) to address priorities of community members, design studies in a culturally-sensitive and participant-friendly structure, implement and disseminate findings into the community, and enhance public trust and participation in research. The CCTSI has built a robust CE infrastructure governed by the **Partnership of Academicians and Communities for Translation (PACT) Council**, aided by 8 Community Research Liaisons (**CRLs**) embedded in diverse racial, ethnic and geographic communities around Colorado and partnered with the Colorado Foundation for Public Health and Environment (now Trailhead Institute), which assists the CCTSI in building research infrastructure in our partner communities. Our CE and Research (**CE&R**) Core, built on the Governance of the PACT Council, includes Educational Programs, Longitudinal Community Relationships, Consultation Services and a CE Pilot Grant Program. These programs are conceptually joined as a pipeline of resources designed to serve investigators and community members seeking to improve community health through translational research. In the next 5-yr grant cycle, the CE&R Core will broaden the stakeholders with whom we engage and further integrate CE&R throughout the CCTSI, our partners in team science at University of Colorado (**CU**), Colorado State University (**CSU**), our hospital partners and the CTSA Consortium. To achieve these goals, we propose the following **Specific Aims:**

Aim 1: Expand our community stakeholders to include the array of healthcare organizations and payers to expand the potential for implementation and dissemination.

Aim 2: Further infuse Community Engagement throughout the translational spectrum within all CCTSI programs and operations.

Aim 3: Increase capacity for bi-directional engagement between researchers and community stakeholders to enhance the science of community-engaged translational research.

***Collaboration and Multidisciplinary Team Science*:** The CCTSI has invested in the advancement of team science through incentives (e.g., leadership training in team science, team science pilot grant awards) that bring together investigators across different scientific disciplines and across different levels of the translational research spectrum to conduct innovative CTR. We will enhance and expand these programs in this proposal by advancing the integration of community stakeholders in CTR research teams and by building a new Science of Team Science (SciTS) program. The SciTS program will be scaled up from activities first developed and evaluated at CSU. The overarching goals are to **foster an environment that values team science research and to develop and evaluate evidence-based team-building activities** that will enhance the success of research teams through the following **Specific Aims**:

Aim 4: Catalyze translational collaboration and team science training and the engagement of community stakeholders with research teams

Aim 4.1. Expand general team building and leadership training programs and establish best practices in team science for local and national dissemination

Aim 4.2. Embed community stakeholders in translational research teams

Aim 5: Implement a Science of Team Science (SciTS) academic program to enhance the success of multidisciplinary research teams

Aim 5.1. Support professional development focused on team science and build capacity to help research teams apply **SciTS** knowledge to their activities

Aim 5.2. Evaluate the effectiveness of facilitated research team-building activities

Common Abbreviations used in this Component

BCT	Boot Camp Translation	CSU	Colorado State University	PACT	Partnership of Academicians and Communities for Translation
CBPR	Community Based Participatory Research	CTR	Clinical Translational Research	PBRN	Practice Based Research Network
CE&R	Community Engagement & Research	CU	University of Colorado	PCORI	Patient Centered Outcomes
CIP	Catalyst for Innovative Partnerships	CU-AMC	University of Colorado Anschutz Medical Campus	PMP	Personalized Medicine Program
CIT	Colorado Immersion Training	GNCR	Great North Care Record	QHN	Quality Health Network
CORHIO	Colorado Regional Health Information Exchange	HANDDS	High Arrest Neighborhoods to Decrease Disparities in Survival	RE-AIM	Reach, Effectiveness, Adoption, Implementation and Maintenance
CPA	Colorado Prevention Alliance	HIE	Health Information Exchanges	SciTS	Science of Team Science
CRLs	Community Research Liaisons	LITeS	Leadership for Innovative Team Science	SNOCAP	State Networks of Colorado Ambulatory Practices and Partners

COMPONENT C: COMMUNITY AND COLLABORATION

RESEARCH STRATEGY – *C.1. Community Engagement (CE)*:

A. SIGNIFICANCE

The PACT transforms translational health research to balance responsibility and power between community, clinicians, and researchers to improve the health of the people of Colorado and the Rocky Mountain Region. Over our first two CTSA grant cycles, CCTSI CE&R has formed a robust infrastructure to elevate patient-centered, practice-based, community-engaged research and training throughout the translational research spectrum (T0.5 to T4) and strengthen the bidirectional links between the academic medical center, healthcare providers, community organizations and other stakeholders. The PACT Council has a truly shared governance structure and applies this shared decision-making to resource allocation within the CE&R Core programs.

Table 1. Community Engagement Vital Statistics

Active Community Partnerships	8 Community Research Liaisons representing 9 Colorado communities 7 Community PACT Council members 5 Practice Based Research Networks Colorado Foundation for Public Health & the Environment
Training Programs	Colorado Immersion Training; Boot Camp Translation Facilitator Training; Let's Get Started: Intro to CBPR for Community-Academic Research Partnerships; Authentic Community Engagement Training; MPH Immersion Field Experience
Programs & Resources	Community Research Consults; CRL Curriculum, CE Seminar Series; Research Exchange; Data Sharing Guidelines
Pilot grants	Partnership Development & Joint Pilot projects with average ROI = 16.9x

B. INNOVATION AND C. PRELIMINARY DATA.

We have made great strides in achieving new initiatives launched during our current grant cycle (Table 4), specifically in the areas of **Boot Camp Translation (BCT**) and **Community Engagement Consults**. BCT addresses the final translational barrier, by taking evidence-based guidelines and recommendations and converting them from scientific, medical language into messages that are accessible and understandable to patients and community members. BCT has been used for >30 medical topics in Colorado and throughout the U.S., with CCTSI, PCORI, & AHRQ funding; 4 BCT facilitator trainings have been held in Colorado, and in Oregon and Saskatchewan. A 2016 invited paper in *Health Affairs*, describes BCT's role in completing the final step of translational research to the community and practice level.

Community Engagement Consults provide expert consultative support for investigators who wish to engage communities in research. Our Community Consults & Ethics Committee, with 13 community and academic members, meets monthly to discuss ethical concerns in community-engaged research and provides consultation to investigators and research teams. One notable consult in 2016 was with our new CU Center for Personalized Medicine, helping to create a Community Advisory Board that will now be a bedrock of this genomics program.

Anchoring our **Educational Programs**, the annual **Colorado Immersion Training** (**CIT**) in CE provides a 9-mo, mentored experience studying Community-Based Participatory Research (**CBPR**) principles, grounded in a 1-week in-depth immersion into one of our partner communities. These experiences are designed and led by our CRLs plus community members and organizations. More than 70 researchers have completed CIT since 2008, 94% of whom reported the program was both professionally and personally transformational and changed their approach to research. The CIT program also includes a "Community on Campus Day" for community members to come to campus for a day to meet with various investigators and program leaders, as well as a one-day field experience in the community for MPH students. In 2016, more than 40 students completed the field experience.

Our tiered **Community Engagement Pilot Grants** Program offers an initial phase focused on Partnership Development providing up to $10,000 for 1 year to convene stakeholders, develop a common agenda and, if successful, to propose a subsequent **Joint Pilot** award providing up to $30,000 to conduct a pilot designed to lead to a larger extramural grant submission. Our CE Pilots have seen remarkable *return on investment* **(Table 2).** Our "Collective Capacity Building Tool" measures the impact of the pilot program on the development of community-academic research partnerships, and demonstrates large shifts in overcoming previously identified barriers to community engagement (e.g., language, mistrust, scheduling conflicts). Our CE Pilot Grant program has been instrumental in impacting health equity as these have tested and developed community-based interventions and programs in our state. Most notable is the HANDDS program addressing Cardiopulmonary Resuscitation availability in urban, diverse communities. This life-saving program is now being disseminated *nationally* through the American Heart Association.

Table 2. CE Pilot Grant Program Return on Investment (ROI): 2010-2014

Pilot Grant Subtype	# Awards	# Follow-on Awards	%Follow-on	Initial Investment	Follow-on Funding $	ROI
Partnership Development	21	15	71%	$198,000	$4,206,850	21.25
Joint Pilot	27	15	56%	$790,613	$12,476,794	15.78
Totals & ROI	**48**	**30**	**63%**	**$988,613**	**$16,683,644**	**16.88**

Our robust **Practice-based Research Networks** (**PBRNs**; State Networks of Colorado Ambulatory Practices and Partners=**SNOCAP**), directed by Dr. Nease, is a key stakeholder partnership. This infrastructure of 5 primary care PBRNs and a statewide local public health agency PBRN reaches >300 Colorado practices with its own active funding portfolio of >$20 million in extramural research support. These PBRNs are at the forefront of work to deliver evidence-based care to all corners of our state, reducing geographic disparities. The AHRQ-funded Evidence Now Southwest project is an example. (http://www.practiceinnovationco.org/ensw/)

CRLs provide essential support to all our activities, including building bridges between health research, clinical practice and community health initiatives while educating both investigators and community members about the value of equitable and participatory research partnerships. CRLs are embedded in the communities they serve and have a unique understanding of their community's assets and challenges. CRLs engage local patients and health providers to identify community health priorities and assist investigators in designing locally relevant studies that address real community, partner, patient and health provider needs.

Over the current grant cycle, the CE&R programs and leadership have **consulted, collaborated and disseminated** our programs **to numerous CTSA Hubs**, including those in New Mexico, Buffalo, Virginia, Oklahoma, California, Oregon, and Wisconsin, and to universities in New York, Massachusetts and Rhode Island. Our CRL, CE Pilot Grant, CIT and BCT programs have been replicated, in whole or in part, across our state and the nation. We will continue to disseminate CE&R models to the Consortium through trainings, presentations and seminars.

We have also made substantial gains in **transforming our institutional environment** into one that supports and values community engagement for academic promotion. With our CCTSI Regulatory Knowledge & Support Core and Office of Grants and Contracts, we have developed innovative policies to allow community members to participate as full partners in our research. These policies and structures will be key assets as we move towards engaging an expanded spectrum of stakeholder organizations and partners (see Aim 2.1).

D. APPROACH

Aim 1: Expand our community stakeholders to include the array of healthcare organizations and payers to enhance the potential for implementation and dissemination of best practices.

Aim 1.1. Reach new stakeholder partners through a new Stakeholder Advisory Board. Recognizing the call to expand stakeholder engagement, we will build on our existing PACT relationships to bring our proven CE&R methods to new health care organization partners. We will develop a **Stakeholder Advisory Board**, which will meet twice/yr with PACT Council and will inform the PACT of opportunities for expanded partnerships, advise on potential new opportunities for CRL placement and assist with the promotion of our CE&R Core activities to a broader group of stakeholders. Planned members are shown in Table 3.

Table 3: New Collaborating Stakeholders for Advisory Board

Colorado Prevention Alliance (coloradoprevention.org) - payers	CPA convenes Colorado payers to work together to advance health. We propose to build on our BCT work with CPA (http://www.coloradopreventionalliance.org/diabetes---depresson-provider-toolkit.html) to further their efforts to address chronic disease and social determinants of health.
University of Colorado Health – health system	As a CCTSI affiliate partner, we will assist UCHealth in community engagement activities to further their service mission to Colorado communities.
University of Colorado Comprehensive Cancer Center – regional cancer center	Through SNOCAP practice-based research networks, we will work with the UCCC Cancer Prevention and Control team to address cancer screening and surveillance cold and hot spots in the locations of our PBRN primary care practices.
Regional Health Extension – public health	We will partner with the Regional Health Extension agent host organizations (CFPHE and Colorado Health Institute) to increase linkages between public health, community engagement and primary care across Colorado.

Aim 1.2. Bridging Community Health Infor-mation with Payers: To appropriately address aspects of health related to social determinants and other issues, it is important to bridge the information gaps that exist between the healthcare and social and public services sectors. We have partnered with colleagues from Newcastle University (UK) who have pioneered a unique sociotechnical infrastructure approach in building out the Great North Care Record (greatnorthcare record.org.uk), which seeks to build infra-structure that will enable all service providers and community members/ patients to access a comprehensive view of an individual's care. Incorporating approaches of Health Information Exchanges (**HIE**) plus community service providers promotes integrated approaches to care and reduces duplication of efforts. We will convene meetings and build out this model across Colorado to explore how it could be implemented here. Partners include CPA, CORHIO and Quality Health Networks (QHN) (our Colorado HIEs), Civic Canopy (a Denver based organization), and Rocky Mountain Health Plans (a Colorado-based payer).

Aim 2: Further infuse Community Engagement throughout the translational spectrum within all CCTSI programs and operations.

Aim 2.1. Integrate with the CCTSI Regulatory Knowledge& Support and Administrative Cores to remove barriers to effective community engagement in research. We have benefited from very close collaborations across the existing cores of the CCTSI with notable examples already mentioned. Our core leadership attends all CCTSI Executive Committee meetings and has participated fully in leadership activities of the CCTSI. In turn, CCTSI leadership routinely attends PACT Council meetings to engage with Council members and CRLs. We will work with institutional leadership to further improve the organizational environment to accommodate community and patient involvement in research, while working closely with other departments, schools, CCTSI Cores and affiliate organizations to provide pathways and support for investigators to pursue community-engaged research. Specific initiatives will include: incorporation of a PACT Council Community representative on the CCTSI Executive Committee, provision of CE and PACT Council input to further the spread of Patient Advocacy Groups (described in the Hub Research Capacity section), and integrate community member input into the Pilot Grant review process beyond the CE Pilot Grant program.

Aim 2.2. Further integrate community engagement into the CCTSI Workforce Development (TWD), Bioethics, and Informatics Cores and in RIC and TIC activities. New opportunities exist for integration and infusion of our engagement expertise within the TWD, Bioethics and Informatics Cores as well as with the RIC and TIC activities already beginning in the CTSA Hubs. Our prior work with BCT will be brought to assist RIC and local recruitment activities. We are experienced as well through our PBRNs in engaging with our partner communities and practices in multisite studies, and this expertise will be brought to bear on RIC activities. Additionally, we will work with TWD to integrate community-engaged research education into the curriculum for all KL2 recipients. Finally, we will assist the Bioethics Core and the Personalized Medicine Program in CE efforts related to participant education, consenting, biobanking and precision medicine.

Aim 3: Increase capacity for bi-directional engagement between researchers and community stakeholders to conduct community-engaged translational research.

Aim 3.1 Build investigator capacity in community-engaged research through education, training and CE&R Pilot Grant programs. Our Colorado Immersion Training, BCT training and Pilot Grant Programs are successful model efforts for developing a highly productive pipeline of translational researchers. We will strengthen and expand and disseminate these programs to other CTSA Hubs. We will also expand our Community Consult program by assisting with grant reviews for CO-Pilot programs.

Aim 3.2. Expand our education and training programs to increase community capacity to engage researchers in equitable research partnerships. Our current efforts to date have largely focused on building capacity among academicians for community-engaged research, with few comparable programs building similar capacity in Colorado communities. To address this gap, we propose the strategies described below:

3.2.a. Education and Training in Translational Research for Community Members and Organizations: Community training opportunities increase understanding about the research process, build trust between University and Community, and enhance community capacity to participate in partnerships with academic investigators. CE&R Core and the TWD program will implement new in-depth programs that provide community-based organizations with training and technical assistance on topics ranging from grant writing and program evaluation to identification and adaptation of evidence-based interventions to improve public health (based on the successful Community Leaders Institute of the Univ. of Cincinnati CTSA). In addition, we have developed a comprehensive training program designed for our CRLs, which includes modules on clinical trials participation, research ethics in community engaged research, and qualitative research methods. This program will provide CRLs with skills to educate their constituents about the benefits of research participation, aligning with our efforts to increase public trust in research and also closely linked to our collaboration with the Colorado Center for Personalized Medicine. We plan to disseminate the CRL curriculum to other CTSAs, via a web-based platform developed with our CCTSI partner, Colorado State University.

3.2.b. Research Readiness: Building upon the training programs detailed above, we will develop a program for certifying community organizations and members as being “research ready” by having completed specific translational research training. This will enable them to more effectively engage with investigators’ proposals as well as increase their capacity to propose research projects in alignment with their own interests. Our pilot is with 2040 Partners for Health, whose Director has served as Co-PI of a successfully awarded PCORI project.

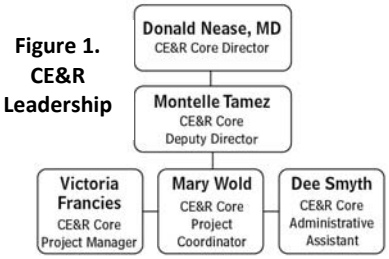
3.2.c. Citizen Scientists: In order to expand our work with T0.5-T2 researchers, the CE&R Core will build collaborations with new organizations, using the Denver Museum of Nature and Science as a pilot. The Museum has an on-site basic science lab and actively engages hundreds of museum visitors in basic science investigation. Their most recent project involved investigation of genetic determinants of taste. Museum visitors learned about the processes of consent, survey administration and completion, and genetic sampling using

buccal mucosa swabs. This outstanding model of engaging citizens in active, basic translational research is one that the Museum is committed to continuing and we will work with them to extend it to other community-based organizations and investigators at our CCTSI institutions.

E. STRUCTURE, GOVERNANCE AND INTEGRATION

The Partnership of Academicians and Communities for Translation (PACT) is the nexus of the CCTSI Community Engagement and Research (CE&R) Core. The PACT encompasses more than 20 Colorado communities, 940 physician practices, 28 hospitals, eight focus communities, 8 Community Research Liaisons, faculty and staff participants from the Colorado Immersion Training in Community Engagement (CIT) program, and core staff. The PACT brings these partnerships into a sustainable and collaborative group for bidirectional exchange, encouraging public trust in the research enterprise while investing in targeted community translational research initiatives. The PACT is operationalized through relationships and strategies deployed by the CE&R leadership (**Fig. 1**) and the governance of the PACT Council (**see Facilities & Other Resources**). This Council is a balanced governance structure of equal numbers of community and academic experts who have equal influence over decisions. The Council oversees statewide initiatives, functioning very much as a non-profit board of directors.

Figure 1. CE&R Leadership



F. TIMELINE AND METRICS / EVALUATION

All Aims will be rolled out in Year one and continued for 5 years. Metrics to be collected, evaluated and reported by our Evaluation Core will include Common Metrics for CE as defined by the CTSA Consortium, plus program specific local metrics. For example, the RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) framework will be applied to CE pilot grantees.

RESEARCH STRATEGY *C.2. – Collaboration and Multidisciplinary Team Science*

A. SIGNIFICANCE

The CCTSI has a strong track record of facilitating and incentivizing the advancement of team science research and removing barriers to its performance (Table 4). Our broad goals are to support inter-disciplinary research collaborations, encourage the appropriate diverse make-up of a team (e.g., statisticians, clinical trials specialists, pharmacists), and educate investigators on how to function effectively as a team. In the next award period, we will place an increased emphasis on building meaningful collaborations by embedding community stakeholders in academic research teams. A transformative new initiative will be the establishment of a Science of Team Science (SciTS) program to improve the effectiveness and success of team-oriented research within the CCTSI and across the CTSA consortium.

Table 4. Collaboration and Team Science Vital Statistics

LITeS	Year-long series of workshops in Leadership for Innovative Team Science – 200 participating faculty
Pilot Grants	Team Science Pilot Grants ($100,000) – 7 recipients CSU-CU Collab. Pilot Grant ($60,000) – 5 recipients CE&R Partnership Dev. Awards ($10,000) – 50 recipients CE&R Joint Pilot Project Grants ($30,000) – 42 recipients
Training	Community Immersion Training CSU-CU Summits I-Corps training program SOM Dean's Interdisciplinary Transformative Awards CSU-CU Natural Animal Models Symposia
Other	Research Studios

B. INNOVATION AND C. PRELIMINARY DATA

The strong commitment of the CCTSI to collaboration and support of team science is evidenced by existing programs that will be enhanced and expanded in this proposal for the next grant cycle (see Vital Statistics Table 4). Some notable innovative examples include the following:

LITeS (Leadership for Innovative Team Science): As an example of the CCTSI **innovations** in promoting Team Science, the TWD program has conducted LITeS since 2008. Judith Albino, PhD, *developed* the curriculum for the annual LITes courses (8 full-day commitments over one yr.), which have included since 2008 more than 200 mid-career and senior faculty from all CCTSI affiliates across all disciplines. LITeS educates about different leadership styles and behaviors, generational differences, and enables development of team-building skills that enhance leadership/managerial abilities and process skills for improving efficiency and quality of a team. Participants are assigned to small teams to work on a 1-yr project of prioritized academic interest. Our thorough evaluation of the program *demonstrate*s its success. A recent team project called *Moving Toward Team Science at CU-AMC* highlighted several institutional challenges for improving the effectiveness of team science: **1)** modify promotion and tenure criteria to be aligned with team research success; **2)** mentor junior investigators who are part of a research team to enable them to pursue both independent and team science; and **3)** dedicate institutional resources to the complex process of building successful research teams. These recommendations will all be addressed in this proposal (see below). The LITeS program has attracted the interest of other CTSA

hubs and will be implemented at Cincinnati and Minnesota CTSA Hubs this year. We plan to actively *disseminate* the program across other CTSA Hubs.

Science of Team Science Program. SciTS research has been conducted at CSU for the past decade. Dr. Jeni Cross and colleagues have found that the strongest teams have central female mentors and that the most successful small teams have equal representation of women and men while the most successful large teams (10+ people) had one-third female membership. Successful teams applied for more and larger grants, enjoyed their interactions, and increased their networks. CSU recently launched a new initiative for developing large interdisciplinary teams: *Catalyst for Innovative Partnerships* (**CIP**), which provides support for professional development in teaming and facilitation of team activities. Newly formed interdisciplinary teams participate in facilitated workshops that raise awareness of the importance of even turn-taking and the roles of women on teams (i.e., scientific leaders, not note-takers). There are also facilitated discussions of research practices and approaches that have been proven effective in increasing self-awareness and mutual understanding among diverse transdisciplinary teams. The CIP has found that these dialogues are especially useful for teams working across the translational spectrum. The structured conversations build team rapport and increase understanding about differences in how team members think about scientific problems, approach research, deal with data, and apply existing knowledge in the field. The CIP program incorporates these topics into training and provides coaching on how to host diverse team meetings in a manner that accelerates the translation of knowledge across disciplines. In addition to leading the workshops, the CIP facilitators participate in team meetings and provide feedback on the team's interactions.

Needs Assessment at CU-AMC: In 2011, the CCTSI Evaluation Core conducted a case study analysis of team science at CU-AMC to examine the associations between team structure, functioning, and productivity among team science pilot grant awardees. Team size was directly associated with translational reach, but inversely related with meeting productivity and research productivity. A team science approach was perceived to lead to more robust research questions, more strategic ways to use limited resources, and better cutting-edge approaches to address questions. Other factors included: early negotiation of responsibilities and authorship; mentors and institutional leaders that champion team science; protected time for clinicians to engage in team science; increased start-up time for complex protocols; and leadership and team-building skills development.

D. APPROACH

Aim 4: Catalyze translational collaboration and team science training and the engagement of community stakeholders with research teams

Aim 4.1. Expand general team-building and leadership training programs and establish best practices in team science for local and national dissemination.

1: Best Practices in Team Science*.* Although activities described above demonstrate strong institutional commitment to Team Science, promotion criteria for Team Scientists have not been established by all of the multiple CU-AMC academic units. For example, the School of Medicine and School of Dental Medicine have promotion criteria recognizing the important contributions of Team Science activities, but the School of Public Health has no such promotion criteria. In his position as the Assistant Vice Chancellor for Clinical and Translational Science, Dr. Sokol, the CCTSI PI, will ensure that **all Schools and Colleges** at CU-AMC transform their promotion criteria along these lines. Through his role as the Director of the CCTSI, this will also be communicated to the affiliate institutions (e.g. NJH, CSU, CU-B).

2: LITeS Program for Junior Investigators and Existing Teams. Although the LITeS program described above has been successful in establishing the value of Team Science, the program has not included junior investigators. However, it is junior faculty who likely experience the greatest challenges when trying to engage effectively in research teams and have their contributions appropriately recognized. To enhance the LITeS program, Dr. Albino has developed a new abridged version of LITeS (LITeS-Lite; 5 weekly 3-hr sessions) that will target graduate students during the next grant period, and which has received support by a BEST award (Broadening Experiences in Scientific Training; DP7 OD018422). We now propose to add another similar program for junior faculty (LITeS-Jr.), who are currently not targeted by either the LITeS or LITeS-Lite programs. We also plan to develop a Team-LITeS program, whereby existing or newly forming research teams can participate in the program. All of these programs will be rolled out during years 1-3 of the next funding period.

3: Promote team science by enhancing the very successful **LITeS program, the Team Science-oriented Pilot Grants,** and other team science programs described above and in grant Component D. Translational Endeavors.

Aim 4.2. Embed community stakeholders in translational research teams

As described in grant section C.1 above, the CE&R Core has facilitated numerous collaborations between academicians and community partners. Almost exclusively, these have been in T3-T4 translational research. A new goal is to embed community stakeholders in research teams that are conducting T1-T2 research. One example of how this will be accomplished is in Aim 3.2.c (Citizen Scientists).

Aim 5: Implement a Science of Team Science (SciTS) academic program

The **SciTS** will involve the iterative and recursive process of collecting data about how teams work together and applying that knowledge to enhance success. Teams that receive two specific types of professional development, *visioning workshops* and *training on teaming*, are more successful than teams that receive one or no training sessions. The CCTSI will support Team Science on multiple levels, including *professional development, building capacity* to help teams apply SciTS knowledge, and engaging in *assessment and evaluation* to test team science intervention strategies.

Aim 5.1. Support professional development focused on team science and build capacity to help teams apply SciTS knowledge to their activities

Professional development and capacity building across the CCTSI will be led by Jeni Cross, PhD (**see Bio-sketch**), who will implement the successful program at CU-AMC that she developed at CSU, including:

1: Team Science Seminars*.* Professional development will begin by holding TS Seminars at CU-AMC to increase awareness of best practices for developing effective interdisciplinary teams. Lecture content will include current knowledge of SciTS, examples of how to adopt team performance concepts, and writing techniques to facilitate the generation of innovative ideas and transfer of knowledge. This seminar series will be widely advertised and held at CU-AMC at least twice per year.

2: Workshops for existing and arising scientific teams*.* Workshops will be held to instruct scientific teams on adopting best practices that evolve from SciTS. Topics will include team vision setting, team interactions and facilitation, and team management. For example, content on facilitation will emphasize that a facilitator can build team rapport and trust, which improves knowledge transfer, and assist the team in behaviors that keep the team focused on knowledge creation.

3: Innovative forums. Innovative Forums will bring together an interdisciplinary group of scientists who have a common interest in a disease or health condition (e.g., obesity), with a goal of forming collaborations that will accelerate translational research. Each grant year, one group will be selected from solicited applications to participate. Multi-stakeholder topics will be discussed using various techniques that have proven to be effective in team science, including design charrettes, where teams develop as many ideas about a topic as possible, and facilitated dialogue, where the goal is new idea generation. The expected outcome of these forums is new research collaborations focused on specific problems identified by one or more investigators.

Aim 5.2. **Evaluate the effectiveness of facilitated team-building activities**

A key component of the new SciTS efforts will be the evaluation of how teams form and perform. Each of the professional development and capacity-building activities described above will include formative, developmental, and summative evaluations. The formative evaluation will use typical evaluation forms to rate delivery and importance of lecture content. The summative evaluation will collect data on how teams interact and perform after participation in workshops or forums. Data on team performance will be collected by a research assistant during team meetings (e.g., track even turn-taking, social sensitivity). Data for social network analyses will be collected to provide feedback about team performance and how to improve. Ideally, these data will be collected before the research project begins, while being conducted, and at the end, to evaluate how the team transformed over time. SciTS approaches will also be evaluated using principles of experimental design for the team science projects supported under mechanisms described in Aim 3.1. Strategies will be developed to compare the success of teams exposed to team science training vs. those with no training.

E. STRUCTURE, GOVERNANCE AND INTEGRATION

The Collaboration and Multidisciplinary Team Science program will be under the directorship of Wendy Kohrt PhD, and will interact closely with our TWD program directed by Lisa Cicutto, PhD. The new Team Science initiatives will be under the leadership of Dr. Jeni Cross, an Associate Professor of sociology at CSU.

F. TIMELINE AND METRICS / EVALUATION

Aims 4 and 5 will be launched in Year 1, working in close collaboration with the CE&R and TWD Programs. The new SciTS program will be integrated with programs that incentivize team science (e.g., facilitated training for one team in Team-LITeS). Our Evaluation Core will develop evaluation plans and local performance metrics for the TWD-related components and will also collect and report Common Metrics developed by the CTSA Consortium. Evaluation of SciTS is described above (Aim 4.2).

COMPONENT D: TRANSLATIONAL ENDEAVORS

PROJECT SUMMARY/ABSTRACT

Translational Endeavors encompasses two critical functions for the proposed CCTSI: the ***Translational Workforce Development Program (TWD)*** and the ***Pilot Translational and Clinical Studies Program (PTC)***. Success in clinical and translational science requires teamwork of individuals with complementary expertise. ***The TWD program*** proposes high-performance oriented, competency-based training and preparation to create a diverse, talented and committed workforce with the capacity to accelerate clinical translational science to improve the health of society. The TWD will provide education and training along a pipeline of programs beginning with students and trainees and extending to include career development for all faculty levels (instructor to professor) and staff (any person working on clinical or translational research). We will achieve these goals through the following Specific Aims: **Aim 1:** Develop and retain a highly qualified interdisciplinary team-focused workforce prepared to conduct rigorous clinical translational research (CTR). **Aim 1.1.** Ensure that the entire CTR workforce receives comprehensive training in Good Clinical Practice, Responsible Conduct of Research, research ethics, and regulatory compliance. **Aim 1.2.** Enhance the CCTSI's Workforce effectiveness as teams by providing professional development initiatives in Team Science, Leadership and Mentorship. **Aim 1.3.** Develop, pilot and evaluate a Career Ladder for Professional Research Assistants to standardize professional development and competencies across their career trajectory. **Aim 1.4**. Close learning gaps identified by the CCTSI Workforce by offering new educational programs in big data/informatics, entrepreneurship, and dissemination and implementation sciences. ***The PTC Program*** will accelerate clinical and translational research through a strategic pilot grant program designed to provide funding for innovative ideas, research methods and collaborations by the CCTSI workforce. The Program will focus on the support of new research that will catalyze the translation of scientific discoveries into treatments, develop new approaches to advance translational science, promote community engagement in translational and team science and foster the development of young investigators in clinical and translational research. We will achieve these goals through the following Specific Aims: **Aim 2:** Implement a comprehensive Pilot Translational and Clinical Studies Program (PTC) to accelerate high quality collaborative CTR throughout the CCTSI partner affiliates. **Aim 3:** Conduct rigorous, transparent peer review of PTC applications to ensure that only projects with the greatest potential impact are supported by the program. **Aim 4:** Establish and implement metrics that will be used to monitor the impact of the PTC. The PTC will provide opportunities to address specific CCTSI priorities and open routes for innovative ideas and development of novel technologies. The Program will promote all disciplines of research and will prioritize research proposals that advance the science of translation. Program impact will be monitored both with NCATS Common Metrics and with metrics developed to meet the needs of the PTC locally.

COMPONENT D: TRANSLATIONAL ENDEAVORS

SPECIFIC AIMS

Translational Endeavors encompasses two critical functions for the proposed CCTSI: the **Translational Workforce Development Program** and the **Pilot Translational and Clinical Studies Program**.

Translational Workforce Development (TWD): Success in clinical and translational science requires teamwork of individuals with complementary expertise. As the technology used to conduct biomedical science has rapidly advanced and regulatory requirements to conduct both human subjects and animal research have expanded, individuals with multiple, diverse skill sets are needed to successfully translate discoveries into improved health. TWD will provide high-performance oriented, competency-based training for a diverse, talented and committed workforce along a career pipeline that begins with graduate and postdoctoral trainees and extends to research staff and faculty at all levels. Our TWD will achieve these objectives through the following **Specific Aims**:

Aim 1: Develop and retain a highly qualified interdisciplinary team-focused workforce prepared to conduct rigorous clinical translational research (CTR).

Aim 1.1. Ensure that the entire CTR workforce receives comprehensive training in Good Clinical Practice, Responsible Conduct of Research, research ethics, and regulatory compliance.

Aim 1.2. Enhance the CCTSI's Workforce effectiveness as teams by providing professional development initiatives in Team Science, Leadership and Mentorship.

Aim 1.3. Develop, pilot and evaluate a Career Ladder for Professional Research Assistants to standardize professional development and competencies across their career trajectory.

Aim 1.4. Close learning gaps identified by the CCTSI Workforce by offering new educational programs in big data/informatics, entrepreneurship, and dissemination and implementation sciences.

D2. Pilot Translational and Clinical Studies: The CCTSI will implement a strategic pilot grant program to accelerate collaborative translational and clinical studies by providing funding for new ideas, methods and collaborations. The PTC seeks to support new research that will catalyze the translation of scientific discoveries into treatments, develop new approaches to advance translational science, promote community engagement in translational and team science and foster the development of young investigators in CTR. To achieve these goals, the PTC will identify areas for potential collaboration, supply both targeted and open funding opportunities that address specific CCTSI priorities to open routes for new scientific ideas, and provide the infrastructure to organize and prioritize resources for collaborative efforts in translational medicine. The goals of the PTC will be attained through completion of the following **Specific Aims**:

Aim 2: Implement a comprehensive Pilot Translational and Clinical Studies Program (PTC) to accelerate high quality collaborative CTR throughout the CCTSI partner affiliates. The PTC will promote all disciplines of research and will prioritize PTC proposals that advance the science of translation.

Aim 3: Conduct rigorous, transparent peer review of PTC applications to ensure that only projects with the greatest potential impact are supported by the program. The PTC will use a two-tiered multidisciplinary rigorous review committee to identify the applications that propose to answer important scientific questions using innovative technologies and novel research methods.

Aim 4: Establish and implement metrics that will be used to monitor the impact of the PTC on scientific discovery within the Institute. Program impact will be monitored both with NCATS common metrics and with metrics developed to meet the needs of the PTC locally.

Common Abbreviations used in this Component

BEST	Broadening Experiences in Scientific Training	D2V	Data Science to Patient Value	PIVOT	Partnering for Innovation Value Optimization and Accelerated Translation
CTR	Clinical and Translational Research	DARE	Diversity in Accelerating Research Excellence	SciTS	Science of Team Science
CLSC	Clinical Science Graduate Program	CFSP	Clinical Faculty Scholars Program	SUMMiT	Summer Undergraduate Minority Mentoring in Translational Science
CO-Mentor	Colorado Mentoring Program	ICDP	Individual Career Development Plan	TOTTS	Team Oriented Training across the Translational Sciences
CSU	Colorado State University	LITeS jr	Leadership in Innovative Team Science Program for Junior Investigators	TWDP	Translational Workforce Development Program
CVMBS	College of Veterinary Medicine and Biomedical Sciences at CSU	OIO	Office of Inclusion & Outreach	PTCP	Pilot Translational and Clinical Studies Program

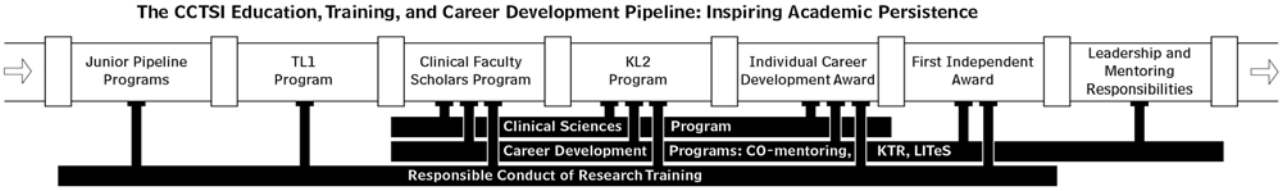
COMPONENT D: TRANSLATIONAL ENDEAVORS

RESEARCH STRATEGY - *D.1. Translational Workforce Development (TWD)*

A. SIGNIFICANCE

Table 1: Vital Statistics
• **Annually, our Clinical Research Education Program has over 700 attendees from across the workforce pipeline (trainees to CTR staff to investigators).**
• **Alumni of CCTSI's primary program for advanced training in CTR (Clinical Science Graduate Program) have received *over 670 grants since graduation and published over 2,500 peer-review manuscripts.***
• **CO-Mentor participants, both mentors and mentees, report better relationships through application of program learning. Attended by 150 mentor-mentee-dyads.**
• **LITeS participants report greater social capital and network reach as a result of program participation.**

Conducting rigorous clinical trials and other CTR has become increasingly complex with the rapid advancement of technology, study design, and analytical methods and the expansion of regulatory requirements. Research teams of individuals with diverse skills sets (from physician scientists to study coordinators and other personnel) are needed to develop, demonstrate and disseminate new treatments to improve health. Continuous education, training and career development for these teams is mandatory. **The CCTSI is building a comprehensive and integrated pipeline of educational programs for attracting, training and retaining a highly competent workforce, which will be fully integrated with our TL1 Training Core and our KL2 Career Development Core.** Our educational pipeline approach (**Figure 1**) for scientists will facilitate synergies in efficiencies, coordination of efforts, and reduce redundancies. The black beams in Fig.1 represent TWD initiatives that support the various stages in career development. This flourishing educational system trains mentors to create a culture of team-oriented science, provides vital protected time to junior investigators, teaches fundamental research and regulatory skills to investigators, coordinators and other team members, and provides essential resources to support proposal development through study implementation. *Specific educational programs will be discussed below and in Components C. Community and Collaboration, I. Career Development Core, and J. Training Core.*



Our educational opportunities will be accessible to <u>all</u> involved in CTR and will provide flexibility to accommodate varied learning needs through rigorous and proven practices[1-6]. Currently in the NIH framework, there are 97 CTR competencies across 14 core thematic areas with an additional 9 sets of role-based competencies. The national CTSA Harmonizing Competencies/ Personalized Pathways Workgroup, in which we participate, is assisting CTSA hub training programs to identify relevant core competencies and the intensity of training for specific research roles and phenotype, while appreciating that not all career pathways require the same depth of knowledge and skill. Our CCTSI TWD will incorporate guidelines produced by this Workgroup that are anticipated in 2018. *Our TWD, which will be fully integrated with our Career Development (KL2) and Training (TL1) cores (***see Components I. Career Development and J. Training Cores***), will provide a comprehensive approach to developing and maintaining a diverse translational workforce ready to meet current and future research challenges*.

B. INNOVATION

To help build a sustainable workforce, we will use a <u>conceptual model of academic persistence</u> as our theoretical framework. Drs. Manson and Nearing (members of our TWD Leadership Advisory Council) developed this integrated model based on Tinto's theory of academic persistence[5-9]. The major tenet is that integration into the academic and social realms of the university strengthens commitment to the institution and the likelihood of scholarly persistence. Participants in many clinical-translational science programs are initially attracted to a research career due to the thrill of discovery, naïve assumptions about autonomy and control over their professional lives, and a desire to make a difference[1]. Without a formalized plan to develop and sustain a research career, their enthusiasm can wane over time. Though characteristics of the learners are important, integration into the academic and social university-CCTSI fabric strengthens commitment and increases the likelihood of remaining in an academic environment and CTR career. Innovative aspects of our educational programs include leadership and interdisciplinary team science emphasis in our didactic and experiential learning programs coupled with the provision of a solid foundation in clinical and translational science training. *In summary, we will maintain an interdisciplinary team science community of learning.*

C. PRELIMINARY DATA/ INSTITUTIONAL ASSETS

1. Existing Resources and Preliminary Data. For a brief description of education and training programs that will be implemented to develop our CTR team-based workforce, please refer to Table 2 below.

2. Needs Assessment. Our Evaluation Core, by conducting needs assessments and post-participant evaluations of faculty, trainees and staff, identified the need for additional formalized training in big data/ informatics, entrepreneurship, and dissemination and implementation sciences. Additionally, opportunities for developing leadership and team skills for junior investigators, including graduate students/trainees, were requested. Finally, our Professional Research Assistants (PRAs) and Study Coordinators requested a formalized structure for career advancement and professional development. All of these will be addressed in this proposal.

D. APPROACH

Aim 1: Develop and retain a highly qualified interdisciplinary team-focused workforce prepared to conduct rigorous clinical translational research.

Key CCTSI educational programs which support the TWD pipeline (Table 2) will be critical for the initiatives within Specific Aims addressed in this component; the target learning audience is also listed.

Table 2: Translational Workforce Development Educational Programs (current and planned)

Program	Description (* will be newly developed, implemented and evaluated))	Audience
Clinical Science Graduate Program (CLSC)	**Aim 1.1 & 1.4**: Lead CU-D graduate program for advanced training in CTR. Grants Masters and PhD degrees and offers multiple courses without requiring program enrolment. Degree programs– 116 students; Course only students – 250/year. *Alumni have held over 370 grants in the last four years, over 670 grants since graduation, and published over 2,500 peer-review manuscripts.*	All CTR Workforce
Clinical Research Education Program	**Aim 1.1**: Curriculum to improve regulatory knowledge and compliance and GCP and RCR application. Provides required regulatory courses (GCP, RCR, human subject protection including informed consent) for all personnel involved in CTR. Offers a variety of training forums: seminars, courses, individual consults, online modules. *Over 700 attendees annually.*	All CTR Workforce
CO-Mentor	**Aim 1.2:** Formal mentorship training for mentor-mentee dyads held over the academic year. *Attended by 60 mentors-mentees/year. Mentors report significant gains (p<0.003) in providing coaching, developing and reviewing individual career development plans, and identifying strengths and gaps in the mentoring team. Mentees report significant gains (p<0.002) in clarity of their career development needs, career path, and next steps, and to establish mutually-agreed upon goals.*	CTR trainees and faculty in mentoring relationships
Leadership for Innovative Team Science (LITeS)	**Aim 1.2**: Comprehensive year long program for effective leadership and building productive research teams. *Annual completion- 30/year. Following the program, over half of participants reported applying their learning a great deal of the time. 70% indicate enhanced social capital, network reach, and connectedness to the institution.* Lead: Judith Albino, PhD	Leaders in the CCTSI including affiliates
LITeS-Junior*****	New program in **Aim 1.2**: Targets junior CTR investigators. Will build team skills and provide resources for action oriented team science. Leads: Judith Albino, PhD & Jeni Cross PhD (CSU)	Trainees (students, post docs, KL2 Scholars)
LITeS-CTR*	**Aim 1.2**: Quarterly workshops will be held to enhance performance of teams and promote resilience. Informed by LITeS and Science of Team Science programs. Lead: Kristen House	CCTSI/CTR Staff (non-investigators)
PRA Career Ladder*	**Aim 1.3**: Standardized training and career development curriculum from entry level CTR Professional Research Assistants (PRA) to Clinical Trials Coordinators. Lead: Alison Lakin, PhD	Research assistants to coordinators

Aim 1.1: Ensure that the entire CTR workforce receives comprehensive training in Good Clinical Practice (GCP), Responsible Conduct of Research (RCR), research ethics, and regulatory compliance. A requirement of all personnel involved in any clinical-translational research throughout our institutions is the completion of the CITI online training modules for HIPAA, GCP, human subject protection, and RCR in addition to attending face-to-face workshops of no less than 8 hours occurring no less than every 3 years. The latter training is available in a variety of modalities: 1) formal 15 week courses in the Clinical Science Graduate Program involving lectures, face-to-face discussions, and applications following NIH recommended curricular requirements (NOT-OD-10-019), 2) lunch hour workshops offered through the Regulatory Core, 3) short courses offered through the Regulatory Core, 4) conference and guest lectures and 5) online modules for self-paced instruction. All CU-D faculty/staff will be able to take any of these courses at no cost through their University tuition reimbursement program. As described in **Components E. Research Methods** and **G. Network Capacity**, CU-D in collaboration with UCHealth and CHCO, will transition the current pre-review and management of study protocols into OnCore (a CTMS) to further streamline processes. We will use the centralized database provided by OnCore to track mandatory training listed above, licensing of and credentialing of research personnel. Members of the research team will only be granted access to OnCore upon completion of the requisite GCP and RCR training. Through these courses and Oncore, standard operating procedures, template forms and checklists will be made available for research teams that can be adapted to meet their needs.

Site initiation visits and periodic audits by RKS will assist researchers in meeting regulatory standards when operationalizing protocols.

Aim 1.2: Enhance the CCTSI's Workforce effectiveness as teams by providing professional development initiatives in Team Science, Leadership and Mentorship. Training in effective team building and implementation will be provided to research team members. **LITeS**, a curriculum for leaders within the CCTSI to enhance effective leadership and research team building skills, will build on its tremendous success. We will leverage our experience in LITeS and will develop **LITeS-like programs** for junior investigators and trainees (**LITeS-Jr**; details **in Component I: Career Development Core**), for entire teams (**Team-LITeS**; details in **Component C: Community and Collaboration**), and for CTR staff and coordinators (**LITeS-CTR**). Quarterly events in these programs will cover topics including working in teams, workforce diversity, managing conflict, working across generations, productive meetings and facilitation and mentoring. **CO-Mentor** (**see Components I. and J.**) is a formal mentor training program for mentor-mentee dyads to attend together for skill development necessary for productive relationships and targets those in formal mentoring relationships.

Aim 1.3: Develop, pilot and evaluate a Career Ladder for Professional Research Assistants to standardize professional development and competencies across their career trajectory. A challenge to retaining a skilled CTR workforce at our institutions is the lack of a robust career pathway for PRAs from entry level to Senior Clinical Trials Coordinator. The CCTSI will address this barrier by developing with our HR departments a new **PRA CTR Career Ladder** in Year 1, to standardize the approach to training and career development and ensure our PRAs are prepared for future CTR needs. Initially there will be 3 career levels: basic, intermediate, and advanced. Qualifications for each level will be determined by a workgroup consisting of inter-organization CCTSI leadership, senior PRAs, HR staff, and members of the Regulatory and TWD Programs. We will: 1) review and standardize job descriptions and expectations to develop a career ladder; 2) standardize initial credentialing and requisite competency training to ensure consistency and provide flexibility to work across CCTSI institutions; 3) develop a curriculum matrix to match competency with training such as consent process, data integrity, managing multi-site studies, etc.; and 4) develop a plan to support and enable PRAs to take professional certification exams of SOCRA or ACRP. An important element of this program will be a Mentorship Program, informed by CO-Mentor, in which Senior Clinical Trials Coordinators will mentor junior PRAs to support those new to the profession and to our institutions.

Aim 1.4: Close learning gaps identified by the CCTSI Workforce by offering new educational programs in big data/informatics, entrepreneurship, and dissemination and implementation sciences. With the emerging importance of Data Science skills in the future of CTR, the TWD program will organize with the Graduate School the following menu of new educational opportunities for research team members. A new Biomedical Data Science Certificate program of 15 credit hours will be initiated in 2018 in response to identified learning needs among research teams. Coursework will include "Introduction to Biomedical Data Science", "Introduction to Biocomputing", "Practical Bioinformatics for Mining", "Computational Methods Addressing Big Data Challenges", "Power of Informatics to Advance Health" and an internship for application of learning. In addition, our CLSC program will add a new area of emphasis, Big Data for Discovery and Decision Support, to prepare the workforce to understand and evaluate big data. Training will include new electives focused on: "Big data-what is it and how to use it", "Analytic methods (data wrangling, deep learning, natural language processing)", and "Big Data: A Team Sport". A second new area of emphasis will be Entrepreneurship, which will be supported by several initiatives. Through the Innovation Ecosystem's I-Corps training program, a team-based short course for faculty, staff and students will guide teams through the stages of customer discovery and an online course addressing commercialization pathways for drugs, devices, diagnostics and tools will be offered (**see Component H2. Innovation Ecosystem: PIVOT**). The Graduate School's NIH funded BEST program will offer two courses, "Introduction to Life Science Commercialization" and "The Legal and Regulatory Environment of Life Science Innovation". The first course addresses fundamentals of commercialization of drugs, devices, diagnostics, and healthcare IT. The second course covers legal aspects of commercialization and regulation. The trainee led Academia Industry Alliance, with CCTSI support, will hold its annual Rocky Mountain Bio-technology Symposium and quarterly Biotech Happy Hours to forge relationships among industry, faculty, and trainees. The final new area of emphasis will be Dissemination and Implementation Science, for which the CLSC will offer 2 new courses: "Mixed Methods in Dissemination and Implementation for Improved Health" covering design, methods and analytical approaches for qualitative and quantitative studies. 2) "Designing for Sustainability" covering conceptual models for sustained behavior change, interventional approaches, evaluative designs, and leadership for change. Short course workshops will also be provided.

E. STRUCTURE, GOVERNANCE AND INTEGRATION

Lisa Cicutto RN, ACNP(cert), PhD will direct the TWD and CCTSI TL1 Training Program and will serve as Associate Director of the CCTSI's KL2 Career Development Program (**For Organizational Chart, see Facilities & Other Resources** and **Components I. Career Development and J. Training Cores**). ***Dr. Cicutto will serve as the CCTSI Liaison to interact with the emerging CTSA network-wide training and staff qualification initiatives***. She holds appointments in the Colorado School of Public Health and the College of Nursing. Her research focuses on developing, evaluating, disseminating and implementing innovative best practice programs to improve the health of people living with lung conditions by partnering with health care providers, individuals and families. She has held consistent external funding as a Principal Investigator since 1998. Since 2008, she has been the Director of the Clinical Science Graduate Program (within the CCTSI). An area of her research program is career development initiatives for health professionals to improve evidence-based practice. She currently serves on and attends the CTSA Workforce Development Task Force. In 2016, Dr. Cicutto was appointed as the CCTSI Director of TWD. To accomplish the aims of TWD, this core will integrate activities closely with the RKS, Community and Collaboration, PTC, Dissemination and Implementation, and Innovation Ecosystem Programs and will work with the Evaluation Core to evaluate the approach outlined in this component.

F. TIMELINE AND METRICS / EVALUATION

All Aims will be initiated in year 1 and continued through the 5 requested grant years. Our Evaluation Core will collect and report Common Metrics to be determined by the national CTSA consortium, and will also perform formal evaluation of our education and career development programs based on local metrics used during the current grant cycle and to be developed (**see Overall Component - Evaluation and Continuous Improvement**). Our Evaluation Core will use these metrics and other evaluation techniques to make recommendations to the Executive Committee for continuous quality improvement in this program.

RESEARCH STRATEGY - *D.2. Pilot Translational and Clinical Studies (PTC)*

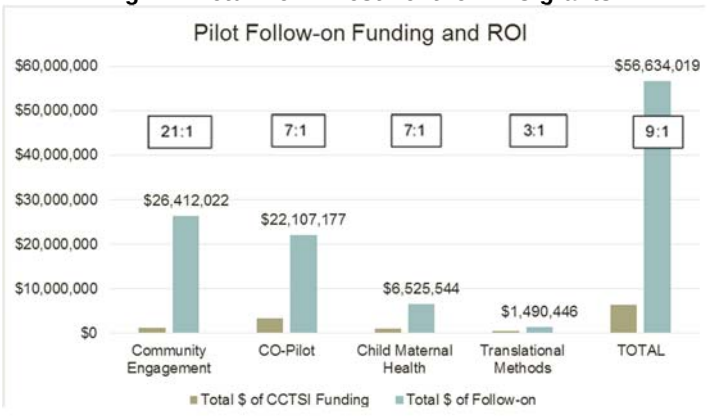
A. SIGNIFICANCE AND B. INNOVATION

The PTC Program of the CCTSI is a vital mechanism for accelerating CTR and team science for the highly competent CTR workforce, created through educational pipeline described in subcomponent D.1. above, by providing funding for new ideas, methods and collaborations, targeted at improved disease prevention, diagnosis, and treatment. The PTC will provide opportunities to address specific CCTSI priorities and to open routes for new ideas, development of new technologies and implement expanded pilot programs. We will tailor our centralized PTC infrastructure to broaden the reach of funding opportunities to encourage integration across the entire T0.5 - T4 spectrum. The PTC will not support basic discovery research; priority will be given to proposals for studies that will provide insights into translational science that could be generalizable to other projects, proposals that have high potential for cross-disciplinary and community collaboration, and for team science initiatives. Through this approach, the PTC will be a vital mechanism for investigators to obtain preliminary data needed for future extramural research grant applications.

C. PRELIMINARY DATA

C.1 Existing Resources. Since inception in 2009, the PTC has received 1,721 applications and given 280 pilot awards for a total of $6.6 million in funding from both CCTSI grant funds and from institutional funds to expand and enhance the impact of CCTSI programs.

Fig. 2 – Return on investment for PTC grants



C.2 Evaluation of current programs. PTC awardees funded from 2009–2014 have generated 0.54 publications per pilot award. Overall Return on Investment (ROI) was 8.9 to 1, with $56.6 million follow-on grants generated from an initial investment of $6.4 million (Fig. 2). In this new grant proposal, faculty at all campuses and hospitals will be eligible to apply for funding through an expanded CO-Pilot program and a new Translational Methods (TM) program, as well as the CMH and CE PTC programs. *A vignette showing PTC program's success follows:*

Case Study: Steven Moulton, MD, a pediatric surgeon at Children's Hospital Colorado, received a PTC award that led to the development of a device that non-invasively monitors hemodynamic changes in central circulatory volume that could result from hemorrhage, dehydration or anesthesia. Dr. Moulton subsequently received $9.5 million in grants from the DOD to further develop this device, now called Compensatory Reserve Index (CRI™), and founded Flashback Technologies (http://www.flashbacktechnologies.com/). Commercial launch of the CRI product is expected in 2017.

D. APPROACH AND E. STRUCTURE, GOVERNANCE AND INTEGRATION

Aim 2: Implement a comprehensive Pilot Translational and Clinical Studies Program

2.1. Structure. PTC will provide $400,000 of support for clinical and translational studies and will serve as a vital mechanism for investigators to obtain preliminary data needed for future extramural research grant applications. *Research that addresses an important translational or clinical research question and also provides insights that could be generalizable to other areas of research will be given high priority for PTC support.* The 4 Programs in PTC will be integrated across Discovery (T0.5-T2) and Community-Population (T3-T4) Translation through 4 distinct programs (**Table1** and below).

Table 3. Pilot Translational and Clinical Studies Programs	Annual Budget	Number of Awards 1st Year	Number of Awards Total
Colorado Pilots	$180,000	5	25
CO-Pilot Mentored			
CO-Pilot Junior			
CO-Pilot Collaborative			
Child and Maternal Health Pilots	$60,000	2	10
CMH Mentored			
CMH Junior			
Community Engagement Pilots	$60,000	2	10
CE Collaborative			
Translational Methods	$100,000	5	25
TM Collaborative			
Natural Models			
Total	**$400,000**	**14**	**70**

2.1.1. Colorado (CO)-Pilots will provide funding for 3 types of pilot projects across all disease areas, all disciplines, and all CCTSI institutions. A total of **$180,000** will be allocated to CO-Pilot annually:

- *Mentored Translational and Clinical Science Awards* ($30,000/award; 2 awards/yr) will provide beginning investi-gators (post-doc fellows, instructors and assistant professors) with mandatory strong multi-disciplinary mentorship and cross-disciplinary training.
- *Junior Faculty Translational and Clinical Science Awards* ($30,000/award; 2 awards/yr) will provide opportunities for junior faculty (Instructors and early-stage assistant profess-ors) to conduct collaborative cross-disciplinary translational and clinical research. Mentorship is not required.
- *Collaborative Translational Science Awards* ($60,000/award; 1 award/yr) will support experienced investigators for projects that require *new cross-institutional (CSU-CU) team science* collaborations. Projects that use natural animal models of human disease as well as other unique CSU resources to overcome existing roadblocks in translation of scientific discoveries will be given priority. This award will require co-PIs from both CSU and CU.

2.1.2. Child and Maternal Health (CMH) Pilots will support cross-disciplinary and cross-institutional research in children, pregnant women and mother-child pairs, which will ultimately improve child and maternal health and prevent diseases that begin in early life. A total of **$60,000** is devoted to the CMH program annually:

- *Mentored CMH Pilot Awards* ($30,000; 1 award/yr) will provide opportunities for beginning investigators to benefit from strong mentorship and cross-disciplinary training in clinical and translational research.
- *Junior Faculty Pilot Awards* ($30,000; 1 award/yr) an opportunity for Instructors or Assistant Professors. #

2.1.3. Community Engagement (CE) Pilots will support meaningful research for communities. A partnership between academic researchers and community organizations or individuals is required. **$60,000** per year will be devoted to fund 2 *Collaborative Pilot Project Awards* for a well-defined joint research project (community-academic co-PIs) that produces preliminary data for future competitive grant applications.

2.1.4. Translational Methods (TM) Pilots will support development of novel methods to address roadblocks in translational research and advance translational science. A total of **$100,000/yr.** will be allocated to the TM program. Two types of awards will be supported:

- *Collaborative TM Awards* ($20,000; 4 awards/yr) will provide opportunities for collaborations to develop new methods, processes and technologies (devices, statistical, digital, science of team science, or bioinformatics) to advance translational science.
- *Natural Models Awards* ($20,000; one award/year) will be an opportunity to form new collaborations to advance the study of spontaneous diseases in animals as models for human disease and human drug and device development. One of the PIs must be a faculty of the CSU College of Veterinary Medicine.

2.2 Governance. Overall leadership for the program will be provided by the PTC Steering Committee, which will be chaired by Dr. Campbell (PTC Director) and members will include the 4 PTC Co-Directors (**see Bio-sketches**): Drs. VandeWoude (CO-Pilot), Hay (CMH Pilot), Nease (CE Pilot), and Serkova (TM Pilot). The Co-Directors, who report to Dr. Campbell, will have primary responsibility for oversight of the specific type of pilot award including solicitation of applications, review process, prioritization of applications, and monitoring productivity. Dr. Campbell will report to the CCTSI Executive Committee and Dr. Sokol, CCTSI Director.

2.3 Fiscal management. A total of **$400,000** of CCTSI grant funds will be allocated to the PTC to support 14 projects per year (Table 1). Each awardee will have an account set up through the CCTSI Administrative Core. Invoices for services, personnel costs, and other expenses will be paid from these accounts. The Core will

provide awardees with reports of spending, balances, and cost management on a regular basis. In recognition of the value of the pilot programs as catalysts for new research, our institutions have agreed to provide support for additional meritorious PTC applications through other funding mechanisms, thus leveraging the CCTSI application and review process.

Aim 3: Conduct rigorous peer review of PTC applications.

3.1. Solicitation of applications. Solicitation for new applications will occur each June and be widely advertised on the CCTSI website, academic announcements from the Deans' offices, and through email to all faculty and trainees at affiliate institutions and community organizations associated with PACT. A "Letter of Intent" by August is mandatory to allow us to choose the appropriate expertise for the review panels, and enable the PTC Program to assist individuals prior to submission of a full application. The application due date (September 15) enables applicants to engage in a thoughtful and collaborative effort toward the application. To ensure compliance with federal and NIH policies, each applicant (when relevant) must describe inclusion of human subjects, model organisms and animal welfare, genetic testing, and/or stem cell research and address the "scientific premise" and "scientific rigor" requirements outlined in the NIH policy on rigor and transparency.

3.2. Review of Applications and decision process. The CO-Pilot, CMH Pilot, and TM award categories have identical criteria for review and evaluation and will use standard NIH review templates and scoring (1-9 NIH scale). Applications will be initially reviewed and scored by a primary and secondary reviewer, which are averaged. A Peer Review Panel, which operates in same fashion as an NIH Study Section (including recusal of reviewers for COIs), will be held in which the most meritorious applications receive full discussion while applications deemed less meritorious will receive a full written review but are not discussed. A separate Peer Review Panel for each category of award ensures review by individuals with the necessary specific expertise. Each application is scored and then ranked by overall impact score. The scores and rankings will then be submitted to the Executive Committee for funding approval. Factors considered in the scoring of the applications are: innovation; scientific merit; cross-disciplinary or collaborative focus; relevance to the CCTSI mission; advancement of science of translation; use of CCTSI resources; investigator/scientific integration; and community participation, if relevant. CE Pilot applications have a unique focus and design and will be reviewed under a separate rubric: The PACT Pilot Grants Committee will review all CE Pilot applications and identify those that have the greatest potential to improve community translation and decrease health disparities. All applicants receive full written reviews of their applications from the two reviewers (primary and secondary).

3.3. Prioritization of Applications. The final impact scores from the Review Panels will be used to set priority for funding. The Executive Committee will receive a formal report from the PTC Co-Director with recommendations for funding based on impact scores. Applications with widely discrepant scores, virtual "ties", and applications which border the funding range and have more direct response to RFAs will be discussed at length. The Executive Committee provides final authorization of funding. ***The PTC will not support clinical trials beyond Phase IIA nor basic research in accordance with NCATS guidelines and PAR 15-304***. Review and approval by NCATs (and IRB or IACUC if relevant) will be performed before funds will be distributed to awardees.

Aim 4. Establish metrics to monitor the impact and outcomes of the PTC.

Tracking progress and outcomes. PTC milestones and monitoring will include: 1) Timely completion of regulatory requirements; 2) Interim (6-month) and final (12-month) progress reports; 3) annual follow-up for three years, using standardized forms from the Evaluation program. Progress reports will describe enrollment and retention of subjects, obstacles encountered, timely analysis of data and dissemination of results. Metrics will include publications, future external funding, patents and novel innovations, publications/presentations, initiation of novel clinical trials and sustained collaboration among awarded investigators. Triennial Needs Assessment Surveys of CCTSI members and non-members of CCTSI will assess benefits and obstacles encountered by applicants, and this feedback will be used to modify the PTC. Novel methods developed by PTC projects will be shared across the CTSA consortium nationally, including the CTSA One Health Alliance (https://ctsaonehealthalliance.org/) for research related to natural animal models of human disease, where appropriate.

F. TIMELINE AND METRICS / EVALUATION

All PTC programs will be initiated in year one and continue through the 5 years. Common Metrics developed by the CTSA consortium for PTC will be implemented, collected and reported (e.g., number of publications per award) and other local metrics will be developed and collected by our Evaluation Core, as outlined in Aim 3. Our Evaluation Core will use these metrics and other evaluation techniques to make recommendations to the Executive Committee for continuous quality improvement in this program.

COMPONENT D: TRANSLATIONAL ENDEAVORS

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COMPONENT E: RESEARCH METHODS

PROJECT SUMMARY/ABSTRACT

The **Research Methods Program** is constructed to support with innovative solutions the design, analysis, ethics, and regulatory challenges that face clinical and translational research (CTR) teams in the complex ecosystem in which CTR research is now conducted. The Research Methods Program is comprised of two Cores: 1) the ***Biostatistics, Epidemiology and Research Design (BERD)*** core and 2) the ***Regulatory Knowledge and Support (RKS)*** core. This program will build upon, share leadership with and collaborate with the corresponding campus-wide infrastructure programs, extending the reach and impact of the CCTSI by leveraging other campus resources to transform our CTR research enterprise. BERD and RKS programs will have co-created activities (Aim 1) that will form a seamless resource for new study design and start-up support for our investigators. The BERD and RKS programs have also identified specific barriers to translation and will develop solutions for removing these barriers, demonstrate the efficacy of these new solutions and disseminate our best practices both within our institution and to the CTSA Consortium (Aims 2-5). The Research Methods goals will be achieved through the following Specific Aims: **Aim 1**: Develop a multidisciplinary Study Jump-Start Clinic to improve the design and analysis rigor and ensure that ethics and regulatory aspects are responsibly addressed in clinical and translational research. **Aim 2:** Develop and disseminate new Methodologies for data analysis including development of new software. **Aim 3:** Develop and promote innovative training and educational resources to encourage rigorous and reproducible designs and analyses in clinical and translational research. **Aim 4:** Promote an efficient, responsible and safe research environment across the lifespan of each study and facilitate improvements in the research enterprise to promote*: Efficiency, Quality, and Ethics.* **Aim 5:** Develop, adapt and disseminate innovative research tools using a regulatory science framework to promote competency. Innovative aspects of this program are an efficient approach to getting investigators together with critical team members prior to submitting a proposal for review, a software development team to enhance analysis methods dissemination, a novel research results dissemination tool kit focused on improving the rate at which study teams provide study results to participants. In addition, BERD and RKS, as our Research Methods Program**,** will facilitate interactions with the Informatics, Ethics, Community Engagement & Research (CE&R) and TIN Liaison Team to assist investigators in optimal use of these resources. The overall result will be an efficient system to enhance research design and analysis and to accelerate the efficiency of the design-to-implementation phase of the translational research process. Successful completion of the aims will transform the clinical and translational landscape, improve the research rigor, and create innovative solutions to design, analysis and regulatory challenges in clinical and translational research. These outcomes will be measured by the Evaluation Core using the Common Metrics and site specific metrics.

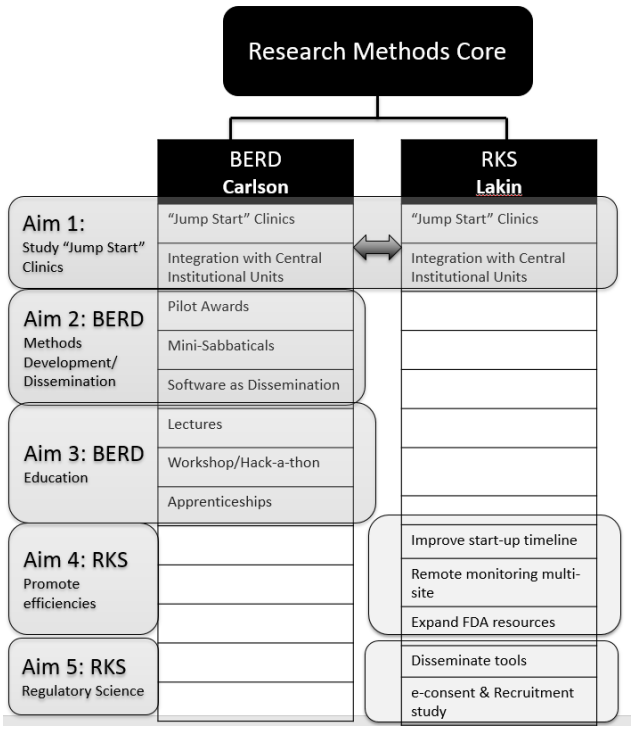
COMPONENT E: RESEARCH METHODS

SPECIFIC AIMS

The Research Methods Program is constructed to support with innovative solutions the design, analysis, ethics, and regulatory challenges that face clinical and translational research (CTR) teams in the complex ecosystem in which CTR research is now conducted.

The Research Methods Program has two synergistic functions: 1) the **Biostatistics, Epidemiology and Research Design (BERD)** program and 2) the **Regulatory Knowledge and Support (RKS)** program (**Figure 1**). These two programs build upon and share leadership with the corresponding campus wide infrastructure programs, extending the reach and impact of the CCTSI programs by leveraging other campus resources to transform the our CTR research enterprise. The programs will have co-created activities (Aim 1) that form a seamless Research Methods resource for investigators. The BERD and RKS programs have also identified specific barriers to translation (described in Approach) and will develop solutions for removing these barriers, demonstrate the efficacy of these new solutions and disseminate our best practices both within our institution and to the CTSA Consortium (Aims 2-5). The Research Methods Program has the following **Specific Aims**:

Figure 1



Aim 1: **Develop a multidisciplinary Study Jump-Start Clinic to improve the design and analysis rigor and ensure that ethics and regulatory aspects are responsibly addressed in clinical and translational research.** We will simultaneously bring together BERD, RKS, and other CCTSI core experts in the clinical and translational sciences to assist investigators at the earliest stages of proposed research. These consultations will result in a project road map and referrals to appropriate resources for more in-depth collaboration.

Aim 2: Develop and disseminate new Methodologies. BERD activities will include a pilot program and mini-sabbaticals to promote methods development and a statistical software team to effectively disseminate new design and analysis tools.

Aim 3: Develop and promote innovative training and educational resources to encourage rigorous and reproducible designs and analyses in clinical and translational research. BERD will develop a pyramid of training offerings that cover general knowledge, hack-a-thons, and expert workshops. The offerings are designed to bring together researchers and other interested parties from different research spaces to bridge the language gaps that often hinder successful team formation and use of state of the art methodologies.

Aim 4: Promote an efficient, responsible and safe research environment across the lifespan of each study and facilitate improvements in the research enterprise to promote*: Efficiency, Quality, and Ethics.* RKS will aim to further reduce approval and start-up timelines with the goal of enabling researchers to move from submission to first enrollment in 80 calendar days or less while ensuring reproducible research.

Aim 5: Develop, adapt and disseminate innovative research tools using a regulatory science framework to promote competency. RKS will use regulatory science methodology to adapt, evaluate and implement new tools, systems and processes to better inform the local and national regulatory environment.

Common Abbreviations used in this Component

BERD	Biostatistics, Epidemiology and Research Design	CTMS	Clinical Trial Management System	IRB	Institutional Review Board
CBC	Colorado Biostatistics Consortium	CTRC	Clinical and Translational Research Center	NIH	National Institutes of Health
CCTSI	Colorado Clinical Translational Science Institute	CTSA	Clinical Translational Science Award	RKS	Regulatory Knowledge and Support Core
CE&R	Community Engagement	CU-AMC	University of Colorado Anschutz Medical Campus	SMC	Study Monitoring Committee
CHCO	Children's Hospital Colorado	IDE	Investigational Device Exemption	TIN	Trial Innovation Network
COMIRB	Colorado Multiple Institutional Review Board	IND	Investigational New Drug	UCHealth	University of Colorado Health System

COMPONENT E: RESEARCH METHODS

RESEARCH STRATEGY – E.1. Biostatistics, Epidemiology and Research Design (BERD)

A. SIGNIFICANCE

Clinical and translational research increasingly involves larger volumes and types of data from a wider variety of sources (cell lines, animals, individual patients, biosensors, electronic medical records, entire populations, and large aggregated data sources), leading to more complex design and analysis elements. This complexity creates a need for larger collaborative teams of experts, who face communication and logistical hurdles. To address these barriers, the BERD program focuses on creating new educational programs that introduce advanced methodologies to investigators in their language. These interactions will allow BERD to identify major design and analysis barriers, develop solutions, and provide a structure to move solutions to broad practice. BERD needs to be fully integrated with other CCTSI resources to effectively identify and intervene in research at its earliest stages of design. BERD and RKS, as our **Research Methods Program,** will facilitate interactions with the Informatics, Ethics, Community Engagement & Research (CE&R) and TIN Liaison Team to assist investigators in optimal use of these resources. The result will be an efficient system to enhance research design and analysis and to accelerate the efficiency of the design-to-implementation phase of the translational research process.

B. INNOVATION

Integrated study design consult service: The major elements needed to develop a rigorous study are often fragmented. The Research Methods Program is developing an integrated **Study Jump-Start Clinic** to bring together BERD, RKS, Informatics, Ethics and community members to assist the investigator. Scheduling has been a barrier to implementing these clinics. In Preliminary Data we show how BERD is using simple online scheduling systems to conduct initial meetings, reducing the time commitment that "office hours" programs entail.

Software as a major dissemination tool: Statistical software is an oft-overlooked aspect of making new methods usable by the research community. Finding individuals who can cross the bridge between methods and software development is challenging. In the past 6 months, BERD has piloted a software development program (see Preliminary Data), which, when full developed in the next grant cycle, will identify common software competencies for BERD package development and launch new tools applicable to CTR studies.

Innovation-Corps™ training: BERD will collaborate with our Innovation Ecosystem Core (see Component H1) to train BERD methodologists in I-Corps™ principles, increasing the likelihood of broad adoption of newly developed methods.

Education program innovation: We will develop educational programs for advanced statistical methodologies that are now commonly used in CTR, including proteomics, metabolomics, structural equation modeling, Bayesian analysis, causal inference, and spatial modeling. Innovative delivery formats will include lecture mixed with literature review, hack-a-thons and software.

C. PRELIMINARY DATA

C.1. Integration of BERD program into campus infrastructure: The BERD is well integrated with the Campus study design and data analysis infrastructure, including shared leadership (Dr. Carlson directs both BERD and the campus wide biostatistics consortium based out of the Colorado School of Public Health). 10 PhD faculty and 2 MS faculty now staff BERD, covering diverse areas of statistical expertise (e.g. Bayesian modeling, microbiome, causal inference, machine learning, structural equation modeling, 'omics, economic modeling, pediatrics, and clinical trials). Over past year, BERD efforts have shifted to focus exclusively on **grant and protocol design and analysis planning**; actual data analysis is supported by the researcher's grants. In the past year, BERD has assisted with 68 study designs for investigators from 16 departments. in every school at CU-AMC. We transitioned 147 projects to analysis through the biostatistical consortium. BERD members are also located at each affiliate campus and hospital to focus effort on study design and project development.

C.2. Piloting an efficient study design and analysis Consult Clinic system - To accommodate shorter questions and assist trainees with design/analysis guidance for their academic products, we have designed an easy access Consult Clinic system that requires minimal online scheduling coordination (see cbc.ucdenver.edu for example sign-up calendars). Sign-ups must occur 24 hours in advance, triggering an email to the consulting BERD member that a meeting has been scheduled. We have piloted this program for all BERD requests. We have had approximately a half-dozen *short* consults. Half of those decided to use the consortium for more in-depth for analysis. Aim 1 expands this Consult Clinic to incorporate other key members for the study design stage (Design/analysis, RKS, ethics, CE&R and Informatics).

C.3. Statistical package development. - Two BERD faculty (Carlson and Mulvahill) completed i-Corps™ training in 2016, resulting in two partnerships with methodologists (Drs. Polotsky/Carlson in Ob/Gyn and Biostatistics; Dr. Kechris in Biostatistics) to develop new software packages for new methods. A third group (Dr. Fingerlin at National Jewish Health Affiliate) has partnered with the BERD to develop a reproducible analysis and methods development pipeline. These investigators self-funded the software development with the BERD contribution used to create training materials for a new short course in software best practices and reproducible research (to be offered June 2017). Example statistical packages can be found at *https://github.com/BayesPulse/pulsatile* and www.github.com/mmulvahill. This work demonstrates our readiness to fully develop a Methods Dissemination Program (Aim 3) focused on disseminating to the CTSA Consortium new validated methods (through newly developed software) for analyzing data from CTR studies.
C.4. BERD education data – We offer a Biostatistics 101 course that enrolls 35-40 students each fall. We are piloting a hybrid on-line/in-class version in Spring of 2017 to be ready to attract a more diverse body using alternative teaching formats. Our first two overview lectures on fMRI and CT brain imaging data (offered June 2016) had 75 and 50 attendees respectively. This demonstrates our ability to attract learners to our education programs and the potential interest that exists for our Aim 3 education programs.

D. APPROACH

Aim 1: **Develop a multidisciplinary *Study Jump-Start Clinic* to improve the design and analysis rigor and ensure that ethics and regulatory aspects are responsibly addressed in clinical and translational research.** The BERD and RKS programs will expand the simple *Consult Clinic* described above (see Preliminary Data) to provide ***easy-accessible*** comprehensive, integrated study design consultations at the earliest stages of research development. The BERD has piloted using Sign-up genius™ web scheduling software to create time efficiency. An investigator fills out a 1-2 minute consult form through a weblink and then immediately receives a calendar of open consult hours. When a request is made, the BERD faculty member assigned to that time slot is sent an e-mail notification. If nothing is scheduled, the BERD member has 24-hour notice that their hour is now free. In the next funding cycle, we will expand this scheduling system to incorporate notification of experts in multiple CCTSI cores (BERD, RKS, ethics, community, and informatics members) for this initial consult of 1-hour with the goal of creating 1-2 slots per week. The investigator will be able to access the request form from multiple website locations (CCTSI website, central campus research resources website, and each individual core website). Both a BERD and RKS member will read each request to vet any issues. In instances where it is clear some expertise will not be needed, the BERD program manager will e-mail those individuals to not attend. The outcome of the *Study Jump-Start Clinic* meeting will be a project plan to ensure that design issues are addressed in parallel. When appropriate, referrals to more in-depth collaboration will be established at these meetings.

The BERD program will also offer ***Design and Analysis Collaboration*** for high priority science. High priority is determined by the following criteria: 1) CTSA TIN referral, 2) high need for design and analysis collaboration (e.g., new data sources, no established design/analysis approach), and 3) large design and analysis component in the proposed project (e.g., high return on investment). Junior investigators will be given priority. Collaborative projects will be identified through four mechanisms: 1) CTSA TIN Liaison Team, 2) *Study Jump-Start* Clinics, 3) online request system (see cbc.ucdenver.edu portal), and 4) campus dissemination (e-mails, seminars). If requests outstrip demand, BERD will work with departments, divisions and the campus leaders to develop new unit specific collaborations. The outcome of these collaborations include budgeted BERD support written into grants for study implementation and analysis.

Aim 2: Develop and disseminate New Methodologies. The BERD will collaborate with the Pilot Translational and Clinical Studies (PTC) and Dissemination/Implementation Cores to promote new methods development.

2.1. Develop Methods: The CCTSI PTC program will re-engineer the former Novel Methods Pilot program to fund innovative methods development grants (see Component D. Translational Endeavors). In addition, to promote novel translational methods development, each year one core BERD faculty member will receive a mini-sabbatical. In January of each year, BERD members interested in a mini-sabbatical will submit a one-page justification of the need for their proposed method and the product to be created during their sabbatical. Proposals will be evaluated and one approved by the BERD Executive Committee. Each BERD member can be awarded at most one mini-sabbatical over the 5-year grant period. Example sabbatical projects include: developing a framework for analyzing sensor data, data integration between 'omics and microbiome and between 'omics and the medical record, and creating new imaging biomarkers from medical images.
2.2. Disseminate Methods: We will work with the Innovation Ecosystem Core (PIVOT) to incorporate I-Corps™ training into the above Development Programs to facilitate an understanding of the market and need for a new method. The major dissemination tool for research methods in the BERD is software. BERD will facilitate

development of software in two ways: 1) build and home grow a team of software savvy design and analysis experts through training and 2) subsidize the prototyping and maintenance of software through collaborative partnerships (see Preliminary Data for examples). These partnerships will be created through internal advertising, the education offerings, and advertising through national groups (BERD SIG in the Association for Clinical and Translational Science and Association of Clinical and Translational Statisticians). We will create an application and review process of proposed partnership formation and use the BERD executive committee to vet the applications.

Aim 3: Develop and promote innovative training and educational resources to encourage rigorous and reproducible designs and analyses in clinical and translational research.

The goal of our education program is to create clinical and translational researchers who understand and can converse in a more complex design and analysis language and to nurture new biostatistician talent capable of communicating with clinical and translational scientists. The training components are:

3.1. BERD Forums: 1 to 2-hour sessions focused on alternating topics to be held monthly: a) Design and Analysis - Behind the Scenes - Inform clinical and translational scientists on the development and implementation of the analytic components of research plans, b) The Basics – The Language of Design and Analysis – A series of basic design and statistics talks that primes scientists to do short and long-course curriculum, c) Fresh and Fierce: New Directions in Design and Analysis - BERD experts and (inter)nationally renowned speakers will discuss developing cutting-edge technologies, studies, and methods, d) I-Corps and Innovation - Presentations by biotech/data science industry representatives, Tech Transfer Office, ethicists and legal experts and e) The Era of Open Science – presentations to Increase awareness of CU-AMC scientists to the importance of reproducibility and best practices.

3.2. Workshops/Hackathons: One Workshop will be held per year. Examples include a sequence of short "overview lectures" on advanced topics (e.g., analysis of imaging data, spatial modeling) or workshops (e.g. open science workshop) targeted at clinical and translational scientists and data experts wishing for a broad overview of a topic. We will also develop Hackathons (e.g., Digital Health Hackathon) that bring together students/analysts solving a problem brought to light by a clinical and translational researcher. This is modeled after the existing `Public Health Case Competitions', where teams of trainees are formed and collaboratively analyze, present, and respond to a presented case in 48 hours. Annually the BERD will elicit questions from clinical and translational scientists. The BERD will register individuals interesting in proposing a solution to emerging data questions (from student pools, campus Centers, regional scientific groups—R user group, American Statistical Association, etc.). On the Friday, the teams are internally formed (by the BERD organization team) from those signed up and the team works over the weekend on the problem. Presentations are Monday afternoon to the clinical and translational scientist who proposed the question. This format fosters science team formation and communication for real-world problems.

Student Apprenticeships: BERD will continue to partner with the campus infrastructure to offer 1-3 full or partial graduate student research assistant positions in graduate training programs that teach the language of collaboration and translational research. This program creates MS and PhD graduates trained in the practical realities of collaborative team formation and who are ready to collaborate with clinical and translational scientists at graduation.

E. STRUCTURE, GOVERNANCE AND INTEGRATION

BERD Director (Carlson) reports to the Research Methods Associate Director (Lakin) (see Component A. Administrative Core and Biosketches). BERD Executive Committee meets bi-annually and consists of members from each affiliate hospital and university, the CHCO Biostatisticians, the Research Methods Director, and an at-large member from the campus-wide biostatistics consortium (currently the Assistant Director). The BERD Director is a member of the CCTSI Executive Committee.

F. TIMELINE AND EVALUATION / METRICS

In Yr. 1: Launch *Study Jump-Start Clinic*, participate in development of Novel Methods Pilot Grant Program, award one mini-sabbatical, offer one I-Corps training session, establish software standards for BERD, recruit new software partnerships, offer reproducible research/software workshops, launch one component of the BERD forums. Yr 2: Maintain Yr 1 programs, launch additional BERD forum, develop and test software, develop Hackathon. Yr 3: Maintain and improve existing programs, launch additional BERD forum, disseminate software and recruit new software partnerships. Yr 4: Maintain and improve existing programs, launch additional BERD forum, develop Hackathon, develop and disseminate software. Yr 5: Maintain and improve existing programs, launch final BERD forum, create national partnerships for software development.

Evaluation will be done in partnership with the Evaluation Core. The BERD will adopt, collect and report Common Metrics as they are developed by the CTSA Consortium. In addition, local metrics will be collected and evaluated by our Evaluation Core, such as the number of *Study Jump-Start Clinics*, number that move to collaboration, number of new methods developed by Pilot Awards, etc.

RESEARCH STRATEGY – E.2. Regulatory Knowledge and Support (RKS)

A. SIGNIFICANCE

To ensure a robust clinical research environment at CU-D and affiliates, it is essential that the RKS Core be ***fully integrated*** with all CCTSI cores to be efficient, effective and successful in facilitating high quality, compliant clinical research. Despite a significant body of work over the past 5 years embedding CCTSI within the fabric of CU-AMC and affiliates, clinical research resources may appear fragmented to the individual researcher who is responsible for having a strong working knowledge of how to access the various regulatory, financial, informatics, approval and educational resources required to optimally conduct clinical research. The CCTSI RKS core and the **Study One-Stop Support (SOS) program** (see Component A. Administrative Core, Quality and Efficiency) will serve as key touch points that will assist the investigator's team in navigating between regulatory, ethics, CE&R and TIN liaison team resources. Given the evolving research regulatory environment, the RKS Core will also embrace the principles of regulatory science, dissemination of new advances and evaluation to make strategic improvements and process changes driven by quantitative and qualitative metrics.

B. INNOVATION

Expansion of Colorado Multiple Institution IRB (COMIRB) to be a regional or national IRB of record: Addressing IRB challenges and concerns for practice-based researchers is a specialized area that COMIRB is well-positioned and experienced to support across the CTSA consortium. Our plan is to work closely with the CE&R Core to serve as the IRB of record for large Practice-Based collaborations locally and nationally.

Mandate a subject recruitment feasibility assessment: In collaboration with the CU-AMC Office of Regulatory Compliance, CU-AMC and affiliates will require all research protocols to include an assessment of the available local subject population (study feasibility) utilizing i2b2 with a user-friendly TriNetx interface (installed by the Informatics Core). The RKS will provide Recruitment Liaisons, modeled on the TIN Recruitment Liaisons, to assist with development of recruitment plans that will be tracked by OnCore (CTMS) and monitored by our institutional Study Monitoring Committee (SMC). The institutional SMC will build on the current CTRC SMC but will have responsibility for the *entire* CU-AMC as well as National Jewish Hospital and CU-Boulder.

Develop an RKS Research Educator: The Denver Museum of Nature and Science, affiliated with the CU School of Medicine, conducts several research studies each year involving several thousand museum visitors as participants, using trained "community scientists". Thus, the museum has been very successful in stimulating the public to participate in research. We will harness this expertise through a broader collaboration that will capitalize on the Museum's educational strategies and resources to train a CU-AMC based Research Educator who will in turn work with our CE&R and RKS Cores to develop and evaluate the impact of new materials and interactive resources to inspire the broader community to participate in clinical research.

E-consent: – The Denver Museum of Nature and Science has also developed an animated pre-consent process that has accelerated their recruitment of research volunteers. The RKS Core, in partnership with the Museum and our CE&R Core, will develop and pilot new software to assist investigators in developing similar tools for E-Consent, and evaluate its effectiveness with the Evaluation Core.

Compare a registry vs. honest broker mechanism at CU-AMC to facilitate recruitment: As outlined in Component G. Network Capacity, CHCO is implementing a patient recruitment database (through consent to be contacted at time of patient registration) to facilitate participant recruitment. In contrast, RKS has been working with the Health Data Compass data warehouse (details in Component B. Informatics) and COMIRB to establish an honest broker program for recruitment of adults at UCH, which will enable researchers who do not have a treatment relationship with potential participants to utilize an honest broker to identify and facilitate contact of potentially eligible patients for their study. In collaboration with BERD and the Evaluation Core, both CHCO and Compass have agreed to design a study to scientifically compare the resources required and the effectiveness of each approach.

C. PRELIMINARY DATA

C.1. Central IRB – Since 1991, COMIRB has been the sole **single IRB** for CU-AMC and its 4 key affiliate hospitals. It is a *national leader* in its approach to working with large Practice-Based Research Networks, which interface with the CCTSI CE&R Core, such as the State Networks of Colorado Ambulatory Practices and

Partners and High Plains Research Network. CU-D and the affiliates have also utilized Western IRB since 2006 for industry sponsored trials. *CU-D signed on to the SMART IRB Reliance Agreement in February 2017*, and is poised to adapt to being a central IRB, or cede to other IRBs when needed, for local researchers to meet the NIH regulatory requirements to utilize a central IRB.

C.2. Centralized resource for investigators: Over the past 3 years, the CCTSI RKS Core, VC for Research office, and UCHealth have created centralized resources to streamline the study approval and contracting process, ensure regulatory compliance, assist investigators with IND and IDE FDA applications, manage ClincalTrials.gov and conduct audits of active research studies. This Clinical Research Support Center will work closely with the new SOS Core, the Ethics and CE&R Cores to expand services and track outcomes. Thus far, the impact of this centralized approach has been a significant reduction in study approval and activation times **(Table 1)**.

Table 1: Study Activation Improvement	2012	2014	2016
Study Activation Time (incl, IRB, contracting, SARC and UCHealth approvals) in calendar days	296	239	120

C.3. CTMS backbone infrastructure investment by the CU-AMC and UCHealth: In the current grant cycle, CU-AMC implemented OnCore as its CTMS, and, while still being phased in for adoption, is now used to manage 2,070 UC Cancer Center protocols and 419 protocols from 10 other research groups, with the plan for all CU-AMC studies to be in the system by 2017. OnCore serves as a document management system, a data collection and subject participation tracking tool, as well as financial management system. CU-AMC and UCHealth have committed to optimizing and fully integrating OnCore by December 2018.

C.4. Broad clinical research education program: The CCTSI Translational Workforce Development Core and RKS have together developed 13 different courses to train researchers and research coordinators on the various complexities of conducting human subject research. A 9 module Responsible Conduct of Research training course is also available to the entire campus annually bringing together clinical, translational and basic science researchers to discuss ethical and regulatory issues concerning research.

D. APPROACH

Aim 1: Develop a multidisciplinary *Study Jump-Start Clinic* to improve the design and analysis rigor and ensure that ethics and regulatory aspects are responsibly addressed in clinical and translational research.

RKS, working with CU-D administration, has streamlined the approval process for clinical research. One of the major challenges is to engage researchers early in the study design process prior to grant submission. The new focus of BERD on study design with the creation of *Study Jump-Start Clinics* (see above) provides a vehicle for RKS, informatics, Community Engagement and Ethics to be involved at that early stage. Along with the BERD team, experienced regulatory experts will participate in the *Study Jump-Start Clinics* to provide expertise on regulatory and operational aspects early on for the proposed research. They will develop a project plan, milestones and a project monitor to ensure that all the regulatory and operational details are efficiently addressed in parallel. This resource will also be used to assist researchers who are interested in designing a multi-site study, working closely with the TIN Liaison program (Component G. Network Capacity). Milestones and timelines will be closely monitored by the Evaluation Core to assess effectiveness of this program (such as time to start-up, meeting accrual, study completion, and disseminating results), allowing for continuous program refinement.

Aim 4: Promote an efficient, responsible and safe research environment across the lifespan of each study and facilitate improvements in the research enterprise to promote: *Efficiency, Quality, and Ethics.*

4.1. Improve start-up timelines: Despite significant efforts over the past 3 years to improve start-up times for clinical studies (now at 120 days), continued barriers to meeting our start-up time goal of 80 days include: the need for closer integration of the SARC scientific review and IRB review processes; harmonizing contract and budget negotiations; expanded regulatory resources to support parallel submission by PIs etc. ***Each of these barriers will be addressed by RKS to meet the goal of an 80-day start-up time by 2020*.**

4.2. Develop and monitor recruitment plans: The RKS team will assist researchers to develop appropriate recruitment plans using local resources and those of the RIC/TIN, which will be monitored by the institutional SMC. Analysis of failing studies by the SMC will be provided to the RKS so appropriate recruitment adjustments can be initiated. The RKS will also oversee the “Subject Information Portal” of actively enrolling studies within OnCore to ensure complete and accurate information is available on the public recruitment website.

4.3. Remote monitoring of multi-site studies: RKS will develop and evaluate novel approaches using OnCore to conduct remote monitoring or risk-based monitoring, to augment traditional site monitoring for multi-site studies both within the TIN and through other funding mechanisms.

4.4. Expand central FDA resources: FDA liaisons within RKS assist investigators with IND and IDE submissions. In 2016, 21 FDA submissions were completed and locally there are 100 approved sponsor IND studies on campus. With our expected TIN-enabled expansion of local PIs designing and conducting multi-site trials, additional tools and resources will need to be developed by RKS to assist investigators submitting multi-site plans to the FDA. In addition, proposed multi-site studies, using our new local CU-D monoclonal antibody and cell-based therapy biomanufacturing GMP facility on the CU-AMC, will require a new level of FDA and regulatory support that will be developed by RKS.

4.5. Use metrics in CTMS: The RKS will use the functionality of OnCore to develop and implement seamless monitoring of study start-up, study enrollment, retention, milestone completion, close-out, etc. and provide routine reports to investigators and the SMC.

Aim 5: Develop, adapt and disseminate innovative research tools using a *regulatory science framework* to promote competency.

5.1. RKS will develop a new **Regulatory Science Toolkit** for investigators and staff using the RE-AIM framework: RE-AIM's 5 elements are: 1) Reach to your intended population, 2) Efficacy of the tools, 3) Adoption by target staff, 4) Implementation consistency, and 5) Maintenance of adoption over time. Reach will include internal (investigators and coordinators), external (research participants), and broad (national adoption of tool) objectives. This framework will initially be used to create and then compare 3 tools for **dissemination of research findings to study participants**. RKS will work with CE&R and Dissemination & Implementation Cores to develop 3 tools (simple letter templates [mailed to investigators vs. just available on the website for use], assist the research team to develop a dissemination package, or RKS to develop a dissemination package). We will randomly select research protocols that will be finishing in yrs 1 and 2 of the proposed grant period to use one of the 3 tools (intervention arms). We will assess and compare across the 3 methodologies: no. of participants contacted, received and "read" the materials; satisfaction with participating in the research study; willingness to participate in another research study, perceived impact of the science; and study team satisfaction with the tool. We will also use a similar approach to evaluate the **e-Consent implementation** process (see B. Innovation above) and **use of TrialSpark** (see Component G. Network Capacity), a software resource to facilitate recruitment.

5.2. Conduct a return on investment analysis assessment at the close of each study in the CTMS: The RKS team will conduct a budget, recruitment and compliance analysis in collaboration with the Evaluation Core of each study at closeout as a quality improvement initiative. The data generated will also be used in aggregate to analyze "success" across the research portfolio for study teams, departments and institutions. RKS will us these data to prioritize tools, enhance educational materials, and educational offerings.

5.3. Implement tools, forms and processes from TIN: These RIC/TIC TIN resources will be adapted by RKS and disseminated to assist local single site or multi-site studies. Conversely, locally developed tools that may be of value to the TIN will be disseminated back via the RKS and TIN Hub Liaison Team. For example, the CTSA Collaborative DSMB Workgroup developed a DSMB Training Manual for investigator initiated studies and are developing an on-line education program to be evaluated for its uptake and utility. Workgroup Members included Barbara Hammack PhD of the CCTSI, Blair Holbein of UTSW, and Tamsin Knox at Tufts.

E. STRUCTURE, GOVERNANCE AND INTEGRATION

RKS will be directed by Alison Lakin, director of the Research Methods Program, who will oversee approximately 1.5FTE staff integrated within CU-D central administration resources. The RKS and TIN Hub Liaison team will continue to meet monthly to coordinate process and assist research teams. The *Study Jump-Start Clinic* team meets bi-monthly to develop process and support. The RKS is also closely integrated with the CE&R and TWD programs. The RKS Associate Director is a member of the CCTSI Executive Committee and reports to the PI and Director, Dr. Sokol.

F. TIMELINE AND EVALUATION / METRICS

All aims will be initiated in year 1 of the new grant cycle and will continue throughout the 5-year grant period. Common metrics developed by the CTSA Consortium will be collected and reported by our Evaluation Core and used to guide continuous improvement. In addition, local metrics will be obtained and used to monitor efficiency and safety, including for example study start-up times and time to first enrollment.

COMPONENT F: HUB RESEARCH CAPACITY

PROJECT SUMMARY/ABSTRACT

The goal of the **Hub Research Capacity** program of the CCTSI is to support clinical and translational research (CTR) that engages diverse communities in projects conducted by investigators from a broad spectrum of disciplines across the CCTSI affiliated institutions. As outlined in the FOA, this component includes cores focused on ***Integrating Special Populations (ISP)*** and ***Participant and Clinical Interactions (PCI)***. The **ISP** core will build on and expand the extensive existing resources and adopt new strategies to engage volunteers in research, with an overarching goal of ensuring appropriate inclusion by age, sex, gender, race, and ethnicity, and from underserved communities. This will be accomplished through the following Specific Aims: **Aim 1:** ensure that infants, children, and adolescents continue to be an important focus of CTR within the CCTSI by supporting research on both common and rare childhood diseases. **Aim 2:** evaluate and promote the appropriate inclusion of older adults in CTR and raise awareness of age bias in research. **Aim 3:** develop a standardized approach for monitoring recruitment success in CTR protocols and strategies to enhance the inclusion of underrepresented minorities. Examples of the approaches to accomplish these aims include: engaging Patient and Advocacy Groups to assist with study design and patient recruitment; supporting research networks focused on improving care for the most vulnerable elderly; and expanding resources, such as tele-technology, to connect with hard-to-reach populations. The **PCI** core will focus its efforts on improving infrastructure and processes that enhance the safety, efficiency, and merit of CTR. This will be accomplished through the following specific aims: **Aim 4:** implement OnCore, a Clinical Research Management System, for all CTR protocols that involve more than minimal risk to human subjects to improve tracking and evaluation of benchmarks of success. **Aim 5:** develop the PCI Management Program, which will provide oversight of centralized research facilities and staff and expand resources to improve the safety, efficiency, and merit of CTR. **Aim 6:** ensure the high quality and scientific impact of the CTR portfolio through rigorous review of scientific merit, monitoring of protocol benchmarks of success, and tracking of dissemination of results. Examples of the approaches to accomplish these aims include: centralize the management of protocol documents for coordinated reviews by the Scientific Advisory and Review Committee, Colorado Multiple Institutional Review Board, and other entities; expand the pool of centrally-trained and –managed research personnel under a fee-for-service model, including research coordinators, budget specialists, and regulatory specialists; and utilize OnCore to monitor protocol-specific benchmarks of success in participant accrual and retention, compliance to the protocol, and safety. The Hub Research Capacity component of the CCTSI is fully committed to building infrastructure and developing and streamlining processes that will enhance the reach and impact of CTR.

COMPONENT F: HUB RESEARCH CAPACITY

SPECIFIC AIMS

The overarching goal for **Hub Research Capacity** is to support clinical and translational research (**CTR**) that engages diverse communities in projects carried out by investigators from multiple scientific disciplines. For ***Integrating Special Populations (ISP),*** this will be accomplished by expanding our extensive existing resources and adopting new strategies to engage volunteers with appropriate representation by age, sex, gender, race, and ethnicity, and from underserved communities. The ISP **Specific Aims** are:

Aim 1: Ensure that infants, children, and adolescents continue to be an important focus of CTR within the CCTSI by supporting research on both common and rare diseases.

1.1. Engage communities and Patient Advocacy Groups as research partners to assist with study design and patient recruitment and to enhance the dissemination of research findings

1.2. Catalyze innovative pediatric research through the CMH pilot grant program, including at least one annual award that targets early origins of chronic disease, and networking events

Aim 2: Evaluate and promote the appropriate inclusion of older adults in CTR

2.1. Utilize the Clinical Research Management System (OnCore) to track the intent to include older adults in research (targeted age range, 60+ y) and evaluate enrollment success rates

2.2. Support research networks focused on improving care for the most vulnerable segments of the aged population, including those who are terminally ill and those in long-term care facilities

Aim 3: Develop a standardized approach for monitoring recruitment success in CTR protocols and strategies to enhance the inclusion of underrepresented minorities (URMs).

3.1. Utilize OnCore to define target populations, capture accrual rates and facilitate standardized reporting on the enrollment and retention of research volunteers, including URMs.

3.2. Expand local resources and technology to assist investigators with recruitment of volunteers for CTR, including hard to reach populations (e.g., culturally sensitive mechanisms, tele-technology)

The ***Participant and Clinical Interactions (PCI)*** component of Hub Research Capacity will be centered on processes that evaluate and set high standards for the quality, conduct, and merit of CTR. **Specific Aims** are:

Aim 4: Implement OnCore to manage & track all human subject protocols with more than minimal risk.

4.1. Centralize management of protocol documents for coordinated reviews by the Scientific Advisory and Review Committee (**SARC**), Colorado Multiple Institutional Review Board (**COMIRB**), and other entities

4.2. Assess protocol resource needs and feasibility through the standardized development of the protocol calendar of events and budget

Aim 5: Develop the PCI Management Program that will provide oversight of centralized clinical research facilities and expand resources to improve the quality, efficiency, and safety of clinical research

5.1. Promote the use of centralized research facilities staffed by trained research nurses and technicians and expand mobile research capabilities within CHCO and UCH

5.2. Manage specialized clinical research resources that require unique facilities, equipment, and/or trained personnel to ensure the quality of data collection and efficiency and safety of operation

5.3. Expand the pool of centrally-managed research/trials personnel under a fee-for-service model, including research coordinators, budget specialists, and regulatory specialists

Aim 6: Ensure the high quality and scientific impact of the clinical research portfolio through rigorous review of scientific merit, monitoring of protocol benchmarks of success, and tracking of dissemination of results.

6.1. Ensure high scientific merit of all protocols involving more than minimal risk to human subjects through peer review by SARC, populated by investigators from the CCTSI affiliates with broad scientific expertise

6.2. Utilize OnCore to monitor protocol-specific benchmarks of success (participant accrual/retention, adherence to the protocol, safety) and ClinicalTrials.gov to monitor updates and dissemination of results

Common Abbreviations used in this Component

BCT	Boot Camp Translation	CIT	Colorado Immersion Training	PACT	Partnership Of Academicians And Communities For Translation
CAB	Community Advisory Board	CRL	Community Research Liaisons	PBRN	Practice-Based Research Networks
CBPR	Community-Based Participatory Research	CTR	Clinical And Translational Research	Scits	Science Of Team Science
CE&R	Community Engagement And Research	HIE	Health Information Exchanges	SNOCAP	State Networks Of Colorado Ambulatory Practices
CIP	Catalyst For Innovative Partnerships	Lites	Leadership For Innovative Team Science		

COMPONENT F: HUB RESEARCH CAPACITY

RESEARCH STRATEGY – *F.1 Integrating Special Populations (ISP)*

A. SIGNIFICANCE. The integration of special populations across the lifespan in CTR is critical for building the foundation of knowledge on which evidence-based medicine can be practiced, and to better understand the early origins of disease, the factors that promote disease development and progression at various life stages, and the potential age-specific effectiveness of therapeutic strategies aimed at prevention or treatment. Similarly, CTR must include underserved segments of the population to advance knowledge of how cultural, socioeconomic, and other factors influence health. Integrating minority populations in CTR is recognized by NIH as a high priority and is monitored at our institutional level (i.e., IRB). However, the CCTSI can play an increasingly important role, by developing and supporting unique methodology to conduct research effectively in special populations. In the next award cycle, the CCTSI will build from our extensive experience and programs in research directed at special populations and place increased emphasis on the promotion of lifespan research. In addition to the following ISP Specific Aims, Optional Function #1 of this application will focus on child and maternal lifespan research (**see Component H2, ELEP**).

B. INNOVATION. Although the CCTSI has long promoted the inclusion of underrepresented minorities (URMs), understudied segments of the population, and hard-to-reach populations in CTR, new innovative strategies will be implemented in the next award period that will 1) encourage collaborations focused on lifespan research, 2) enable the tracking of failure/success in the inclusion of special populations in research, and 3) provide new mechanisms to assist investigators with design of experimental approaches that meet needs of special populations and with the recruitment of special populations. We are committed to instilling in investigators the need to include special populations in clinical trials and research.

C. PRELIMINARY DATA and D. APPROACH

Aim 1: Ensure that infants, children, and adolescents continue to be an important focus of CTR within the CCTSI by supporting research in both common and rare diseases

Preliminary Data: In 2016, CHCO was ranked in the Top 10 Best Children's Hospitals (*US News World Report*) and the Department of Pediatrics of the CU SOM was ranked #1 in NIH grant funding for pediatric departments in medical schools (*Blueridge Institute*), reflecting the outstanding quality of research in child health within the CCTSI. The CCTSI manages both the CHCO CTRC and the Perinatal CTRC, which provide state-of-the-art research facilities and experienced research staff essential for conducting high quality, innovative and impactful CTR in infants, children, and adolescents in a safe and compliant environment. The Perinatal CTRC provides mobile services that enhance the safety and efficiency of research in pregnant women and their newborns. Access to these vulnerable (and limited) populations must be carefully controlled; this is managed through the Perinatal Research Facilitation Committee (PRFC), which reviews the feasibility of research protocols, and the Perinatal CTRC, which oversees recruitment of pregnant women and newborn infants. In the past 5 years, the CHCO and Perinatal CTRCs have supported an average of 98 and 26 protocols per year, respectively, with an average of 2,596 and 1,916 visits per year. Under our new subsidized fee-for-service model, these units will provide new services in the next award period (**see PCI sub-component below**).

Aim 1.1. Engage members of the community and Patient Advocacy Groups (PAGs) as research partners. Based on feedback from the 2015 CCTSI Needs Assessment Survey, investigators need support for recruiting research volunteers. New strategies for recruitment that will utilize the electronic health record and i2b2 are described in Component B. Informatics. Another recruitment strategy that will be emphasized involves strengthening of community links. Although most prior CE&R Core initiatives for building partnerships between investigators and community members have been focused on adults, establishing such partnerships is even more critical for pediatric research. Engaging community members with a vested interest in childhood diseases in the early stages of research project development can help to ensure that the experimental approach is designed in a way that minimizes barriers to participation, as perceived by children and their parents. Keeping community members engaged on a research team as a study progresses will lead to new strategies for recruitment of participants and effective mechanisms for the dissemination of study results to the community.

Approach: Long-lasting partnerships will be established between research teams and PAGs. We will work with the PACT Council (CE&R program) to develop a new Child/Maternal Research Committee to explore best practices for educating communities about the value of pediatric and pregnancy research. We will develop a strategy to reach out to PAGs to form new partnerships with the CCTSI. Since many pediatric investigators have established close working relationships with PAGs, we will engage several of these investigators to assist the Committee in developing an inventory of best practices for engaging PAGs as partners in research. We will then

engage active pediatric research groups that do not have such relationships and offer to facilitate these best practices with an appropriate PAG. Our Evaluation Core will determine if a new relationship is formed and its effect on study design and participant recruitment. Best practices identified and demonstrated to be effective will be disseminated to other CTSAs through the *Integration Across the Lifespan* DTF.

Aim 1.2. Catalyze innovative pediatric and lifespan research through the CMH Pilot Grant Program and networking events. The CCTSI CMH pilot grant program supports innovative CTR in children of all ages, pregnant women, and mothers of infants. Mentored awards are open to postdoctoral fellows, instructors, and assistant professors, and junior faculty awards are open to instructors, assistant professors, and associate professors. At least 5 projects at $20,000 per project have been supported annually, with a ROI for follow-on grant funding of 6.7:1. In the next award period, a new emphasis in the CMH program will be Lifespan research (**see Component D. Translational Endeavors).** Research in this area will be catalyzed in several ways:

Approach 1: We will allocate $60,000 per year for CCTSI CMH pilot grants. The grant review criteria and the rigorous review process are described in **Component D**. Grants will be awarded based on merit, innovation, and likely impact. Awardees will present their work at one of two CCTSI-sponsored Pediatric Research Poster Sessions held each year at CHCO, which attract 80-120 posters and 250-300 attendees per session.

Approach 2: At least one CMH pilot grant annually will support a project specifically focused on Lifespan Research. We will prioritize studies that examine how the intra-uterine environment affects fetal development in a manner that can have lifelong consequences, but that can be measured by short-term outcomes in infancy.

Approach 3: Beginning in 2013, when CSU was added as an affiliate member of the CCTSI, there has been an annual 1-day CCTSI CU-CSU Summit at a location equidistant to CU-AMC, CU-Boulder, and CSU, with the intent of stimulating networking opportunities and fostering research collaborations across campuses and disciplines. Attendance has been 90-120 individuals. Summits have focused on specific research topics (e.g., *Precision Medicine & the Use of Omics Technologies* and *Regenerative Medicine & Stem Cell Biology* in 2016. In 2018, the Summit will focus on Early Origins of Chronic Disease and Lifespan Research.

Aim 2: Evaluate and promote the appropriate inclusion of older adults in CTR

Preliminary Data. According to the Administration on Aging, there were nearly 57 million adults aged 60 yr or older in the U.S. in 2010, yet older adults are often excluded from clinical trials, creating a gap in evidence for use of new medications in this age range. Of randomized controlled trials published from 1994-2006, 40% excluded older adults based on age, and this was poorly justified in 78% of trials[1]. Currently, the only mechanism to evaluate inclusion of older adults in CTR is age range specified in the protocol. Further, although investigators report on recruitment and retention for IRB continuing review, this is not done in an age-specific manner, even when there is enrollment in distinct age categories. Thus, there is no efficient way to track either the intent of investigators to enroll older adults, or whether older adults have been successfully enrolled and retained in CTR.

Aim 2.1. Utilize OnCore to track the intent to evaluate the inclusion of older adults in CTR. The implementation of OnCore (see Aim 4 below) will make it possible to collect detailed information on the age at enrollment of research volunteers across all studies at our center.

Approach: Strategies will be developed for monitoring the intent to enroll older adults in CTR and for tracking enrollment success. A standardized report format will be developed that includes metrics on overall enrollment success and targeted areas of enrollment success (e.g., older adults, URMs). These reports will be reviewed by the CCTSI Safety Monitoring Committee (**SMC**), which does an annual review of all protocols conducted within the CTRC Network. An **Aging Research Working Group** will be established by the SMC to: **1)** evaluate recruitment and retention of older adults in CTR; **2)** determine whether age bias is apparent in protocols; and **3)** meet with investigators to discuss reasons for age bias (i.e., sponsor- vs. investigator-driven) and strategies for improving the representation of older adults in CTR, which will be tracked over time by our Evaluation Core.

Aim 2.2. Support research networks focused on improving health care for the most vulnerable segments of the aged population

Preliminary data: Older adults are commonly excluded from clinical trials because of multiple co-morbidities or functional impairment, yet it is these most vulnerable elderly that account for the majority of health care utilization and are the most challenging to treat. Investigators at CU-AMC have established unique national networks to facilitate research in this special population to improve **1)** palliative and end-of-life care (Palliative Care Research Cooperative; **PCRC**), and **2)** care for frail and disabled elderly in long-term care (**LTC**) facilities (Colorado LTC Research Partnership; **LTCRP**).

- *PCRC.* The PCRC is a NIH-supported (U24 NR014637) network that has 3 objectives: **1)** develop palliative and end-of-life care research capacity nationally through provision of infrastructure, data systems, and

metrics; **2)** support the conduct and dissemination of high-quality interdisciplinary research; and **3)** train and mentor new clinician-scientists committed to advancing palliative and end-of-life care research. The PCRC is led by Executive Committee Co-chairs Jean Kutner, MD (Professor of Medicine, CU-AMC, and Chief Medical Officer, University of Colorado Hospital) and Christine Ritchie, MD (Professor of Medicine, UCSF). As of September 2016, the PCRC had 283 investigator members at 120 organizations across the U.S. Primary Coordinating Centers are locate at CU-AMC, Duke University, and UCSF.

- *Colorado LTCRP*. Research to improve health care for elderly in LTC facilities is critical, to both improve quality of life and reduce the economic burden of healthcare utilization. Numerous barriers limit the ability to conduct high quality research in LTC facilities (e.g., disruption of facility routines; legal concerns; difficulty obtaining informed consent). The impetus to form the LTCRP arose from the need of Rebecca Boxer, MD (Associate Professor of Medicine, CU-AMC) to engage LTC facilities in *A Trial of Heart Failure Disease Management in Skilled Nursing Facilities* (NIH R01 AG053413). Recognizing the value of having successfully assembled the facilities, a CCTSI Community Engagement pilot grant was used to form the LTCRP and its Stakeholder Advisory Board (LTC residents, family members; LTC corporate representatives; LTC staff, medical directors; investigators; state regulators; ethics scientists). This led to a successful PCORI award to Dr. Boxer to use the LTCRP to advance LTC-based comparative effectiveness trials. Goals of the LTCRP are to: **1)** promote innovative LTC-based research; **2)** review proposals for LTC-based research and provide recommendations on merit, feasibility, and barriers; and **3)** facilitate the conduct of LTC-based research.

Approach: The LTCRP was formed to support local research in LTC facilities. One link that will be developed is with the PCRC, because that group has had limited success conducting research in LTC facilities. This is expected to elevate the visibility of the LTCRP at a national level. In fact, the LTCRP has already had inquiries from investigators at remote academic institutions regarding utilization of the network of LTC facilities assembled by Dr. Boxer for trials that are not meeting accrual targets. The CCTSI will support the PCRC and LTCRP by disseminating information about their resources, through links on the CCTSI website and e-newsletters, and through the Lifespan DTF of the CTSA Consortium and through the Trial Innovation Network infrastructure.

Aim 3: Develop a standardized approach for monitoring recruitment success in CTR protocols and strategies to enhance the inclusion of underrepresented minorities

Preliminary Data: Currently, investigators develop their own approaches for recruiting and maintaining records on the enrollment and retention of URMs, which are reported as part of continuing IRB review, thus enabling evaluation only on a protocol-by-protocol basis. There is no system-wide approach for tracking and reporting the inclusion of URMs at the institutional level. Developing such approaches will identify research groups that excel in this and, by identifying and disseminating their best practices across other studies, will be expected to lead to more widespread success in the inclusion of URMs in research.

Aim 3.1. Utilize OnCore to define target populations, capture accrual rates and facilitate standardized reporting on the enrollment and retention of research volunteers, including URMs.

Approach: Having all clinical research protocols utilize OnCore for study management will provide an efficient mechanism for tracking enrollment and retention. Future plans to integrate OnCore with the IRB management system by linking data exports with IRB continuing review applications is expected to motivate wider use of OnCore. As utilization of OnCore expands, the Clinical Research Support Center and SMC will establish a standardized approach for reviewing enrollment status of protocols, establishing a benchmark that will be considered acceptable progress (e.g., 80% of accrual target), and a process for handling clinical protocols that are not making acceptable progress (e.g., meet with Chair of the Safety Monitoring Committee). The CCTSI will work with underperforming investigators to make them aware of strategies that can be used for recruitment, such as those listed on our webpage on Recruitment of Research Participants, those that will be accessible through the RICs, and those developed by our own CCTSI Trial Innovation Network Liaison Team.

Aim 3.2. Expand local resources to assist investigators with recruitment of volunteers for CTR

Approach 1: The CCTSI is evaluating resources to enhance the recruitment of research volunteers. For example, we are currently evaluating recruitment services from Trialspark, a vendor that utilizes novel methods of maximizing social and online media to target specific demographics. We are subsidizing the cost of this service for 3 ongoing protocols that target diverse study cohorts. If Trialspark proves to be effective, it will be promoted to CCTSI membership and the CCTSI will negotiate with Trialspark to get discounted rates of service.

Approach 2: The CCTSI will also expand its support to investigators to engage hard-to-reach cohorts through tele-technology. Currently, the number of tele-technology stations available to investigators to conduct research

testing is limited. We will add tele-technology capability to the outpatient CTRC and initiated training in its use to make this widely available to investigators.

Approach 3: The CE&R Core has developed the Boot Camp Translation (BCT) method to engage community and patient stakeholders in designing culturally and community sensitive messaging and campaigns to bring these communities into partnership to advance translational research. Our Community Research Liaisons are also a key resource both in support of BCT and to link investigators to diverse communities in Colorado. Both will be employed to engage under-represented populations and communities in clinical trial enrollment.

E. STRUCTURE, GOVERNANCE AND INTEGRATION. As illustrated in the organization and governance chart (Component A. Administrative Core), Drs. Hay (Professor of Pediatrics) and Kohrt (Professor of Geriatric Medicine) will be co-leaders of ISP.

F. TIMELINE AND METRICS / EVALUATION Approaches for ISP will be implemented in yr 1 and continued through the award period. OnCore is being phased in across academic units and centers, and it is planned that this will be system-wide by yr 3. Common Metrics established by the CTSA Consortium and other local metrics developed by the Evaluation Core will be adopted, collected and reported, and used for continuous improvement.

*RESEARCH STRATEGY - F.2. P*articipant And Clinical Interactions *(PCI)*

A. SIGNIFICANCE. CCTSI has an exceptionally strong track record in ensuring high quality in the conduct of CTR in all age participants through the resources and oversight provided by the Clinical and Translational Research Center (**CTRC; clinical research unit**) Network. The CTRCs includes inpatient and outpatient units at UCH and CHCO, the perinatal mobile CTRC, and outpatient CTRCs at NJH and CU-B, providing investigators access to state-of-the-art facilities, highly trained personnel and resources, now in a fee-for-service model. Our hospital partners provide space and support many essential personnel (**see Facilities & Other Resources**).

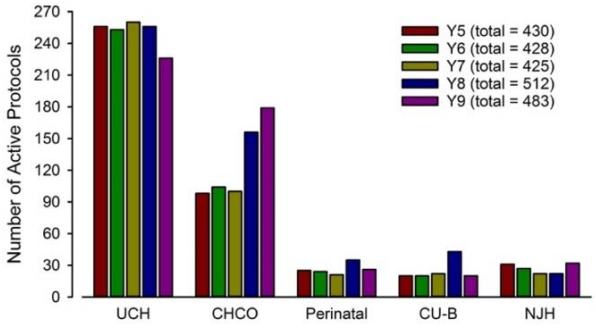


Figure 1. Number of Active CTRC Protocols

B. INNOVATION. The CTRC Network is continuously improving processes to enhance the safety, quality, efficiency, and cost effectiveness of CTR, including single- and multi-site NIH- and industry-sponsored clinical trials. CTRCs will be the backbone for trials conducted within the Trial Innovation Network. The fee-for-service model that was adopted 4 yrs ago will continue to evolve under a new PCI Management Program (NIH NOT-TR-17-012). Junior investigators, who may be disadvantaged by a fee-for-service model, will be supported through *MicroGrants* under the PCI Management Program to help cover costs of CTRC services.

C. PRELIMINARY DATA. The CTRC Network has supported an average of 303 investigator-initiated and 153 industry-initiated protocols per yr over the past 5 yrs; the number of active protocols has remained robust (**Figure 1**) *despite full implementation of a fee-for-service model in yr. 7*. Combining all units, outpatient activity averaged **17,954** visits/year (**Figure 2**) and inpatient averaged **551** days/year at UCH and **279** at CHCO. Outpatient CTRCs were used by 145 PIs (35 academic units) and Inpatient CTRCs by 75 PIs (27 academic units). *The use of these dedicated research facilities and experienced professional research staff ensures the highest level of attention to safety and data integrity and maximizes efficiency*. Based on the 2016 Needs Assessment Survey, the use of the CTRC Network is expected to increase over the next 5 years**.** We will strive to continuously improve protocol approval times and the delivery of CTRC services.

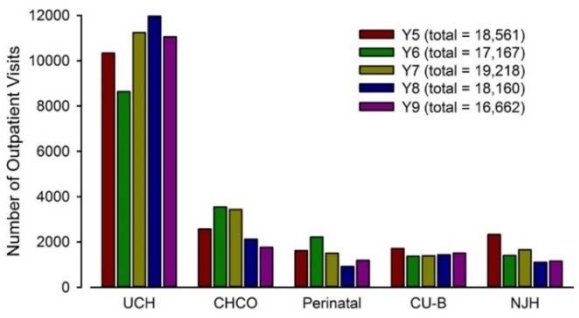


Figure 2. Number of Outpatient CTRC Visits

D. APPROACH

Aim 4: Implement OnCore to manage & track all human subject protocols with more than minimal risk

The OnCore Clinical Research Management, Bio-specimen Management, Epic Demographic Interface, and InfoEd Interface Modules were launched in 2015. Planned deployments include the Epic Billing Grid, Epic Labs, Study Information Portal, and Unified Registry Module. Staged implementation of protocols in OnCore is ongoing. Migration of >1500 Cancer Center protocols to OnCore was completed in 2016. Currently, we are bringing all CTRC Network protocols into OnCore. The final stage, to start in 2018, will bring **all new protocols** that involve more than minimal risk to human subjects at CU-AMC into OnCore. This broad utilization of OnCore will enable the CCTSI to develop recruitment goals and track enrollment; identify scientifically or ethically flawed studies;

institute timely closure of studies; and improve efficiency of study workflows.

Aim 4.1. The Single Portal: Centralized management of all protocol documents. A streamlined process for routing clinical research protocols through the regulatory approval process by using a single application online portal was adopted in 2015. A Protocol Assessment Form (**PAF**) and the Protocol are submitted and provide information that determines which entities must approve the protocol. Now occurring ***in parallel*** are the review of scientific merit (by the SARC) and the evaluation of study feasibility. Once the merit and feasibility are approved, the Protocol undergoes IRB review.

Aim 4.2. Assess protocol resource needs and feasibility. Currently, the evaluation of resource needs and feasibility of a protocol is a tedious and non-standardized process. With a streamlined workflow through OnCore, the calendar of study events will be generated upon which the study budget for all tests and procedures will be developed, including whether they are being done as standard of care or research, which will improve compliance with billing regulations.

Aim 5: Develop the PCI Management Program that will provide oversight of centralized clinical research facilities and expand resources to improve the quality, efficiency, and safety of clinical research

The CCTSI will continue to oversee the management of the clinical research facilities in the CTRC Network (described above) and expand resources that improve the efficiency and safety of CTR.

Aim 5.1. Promote the use of centralized research facilities and trained personnel. NIH restrictions on use of CTSA grant funds may result in increased costs to investigators, with the unintended consequence of driving research away from the CTRCs and making investigators less competitive for external funding. Although we will still charge investigator grants for all services, we will promote use of the CTRC Network and the expertise of CTRC staff in several ways: **1)** Continue to subsidize the cost of CTR services delivered through the CTRC Network with local resources; **2)** The PCI Management Program will provide *MicroGrants* of up to $10,000/yr for up to 3 yrs to junior investigators conducting meritorious research that can be used to pay for CTRC services (nursing support, nutrition services). The *MicroGrants Program* will be supported by the CTSA grant, UCH and CHCO. CTRC Protocols undergo a review of feasibility and scientific merit and, if acceptable in both categories, are considered for *MicroGrants* support; **3)** Expand mobile unit services (e.g., nursing, phlebotomy) to better enable investigators to combine research visits with standard care visits in hospitals or clinics; and **4)** Allow research teams to conduct study visits in CTRC facilities using appropriately trained members of their own team who have been certified by the Clinical Research Support Center (**See Component E. RKS**).

Aim 5.2. Manage specialized CTR resources. The CTRC Network will support specialized research services that require unique facilities, expensive or sophisticated equipment, and/or trained personnel to ensure the quality of data and efficiency and safety of operation. These include: **1)** Bionutrition Core, with services ranging from dietary assessments to provision of research meals; **2)** whole-room calorimetry for 24-hr (or longer) measures of energy expenditure and substrate oxidation; **3)** sleep-related research laboratory; **4)** Cardiovascular Bioimaging Core, for cardiac and vascular ultrasound procedures; **5)** Body Composition Core, for total and regional assessment of lean, fat, and bone mass; and **6)** exercise testing and training research facilities. Each CTRC unit is overseen by a Nurse Manager who ensures the training and credentials of staff and safety of unit operations, and a Medical Director. The Nurse Managers work closely with the Research Subject Advocate to address safety concerns and maintain current standard operating procedures. The Nurse Managers, Medical Directors and core directors meet monthly to discuss CTRC operations with the CCTSI Director of Operations (Janine Higgins, PhD), Associate Director of Hub Research Capacity, and Business Administrator.

Aim 5.3. Expand the pool of centrally managed research personnel under a fee-for-service structure. The CHCO Research Institute and UCCCC provide a pool of study coordinators, budget specialists, and regulatory specialists for investigators conducting clinical trials under a fee-for-service model. This service has not been available at the UCH CTRC but was identified as a high priority in the 2016 Needs Assessment Survey. In December 2016, the UCH CTRC hired a Manager and a Research Coordinator to launch a new UCH **C**linical **Re**search **S**upport **T**eam (**CReST**), which will be gradually expanded as demand increases and be integral to our Study One-stop Support (SOS) concept (**see Component A. Admin Core, Quality and Efficiency**). Initially, services will be limited to Study Coordinator support for clinical trials, including NIH- and TIN-supported trials. As demand grows, personnel will be expanded to include budget and regulatory specialists. CReST will be responsible for credentialing and oversight of personnel, ensuring compliance and operational excellence.

Aim 6: Ensure the high quality and scientific impact of the CTR portfolio through SARC review

Aim 6.1. Ensure high scientific merit of all protocols. The SARC has been a component of the CCTSI since 2008. In 2015, SARC assumed the responsibility of evaluating the scientific merit of all CU-D clinical

research protocols, regardless of whether they utilize the CTRC Network, as well as the financial and practical (e.g., access to the target population) feasibility of conducting a protocol successfully. Protocols deemed not feasible do not undergo IRB review. Despite the serial review by SARC and COMIRB, this process has reduced the time to COMIRB approval by excluding protocols that will not be successful or that have been evaluated as having low scientific merit from the COMIRB slate. Over the past 4 years, the average time from COMIRB submission to approval has been 40 to 45 calendar days, compared with ~150 days 5-10 years ago.

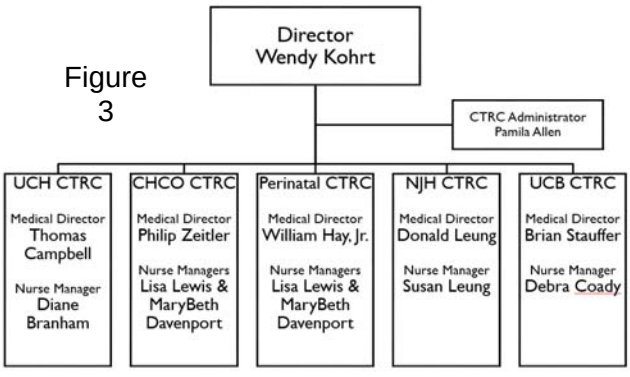
The SARC has two rigorous review mechanisms: **1)** Protocols that have undergone independent peer review of merit (e.g., by NIH) and have not changed substantially since the review are put through an expedited, or **e-review**. This includes evaluating feasibility by the clinical entities that will be involved in conducting the trial (e.g., research nursing) and a rapid scientific review by one of the four SARC Co-chairs. E-reviewed protocols are presented by the Chair at the next SARC meeting for committee discussion and approval. **2)** All other protocols undergo full SARC review, which includes feasibility and scientific reviews by a Co-chair, 1 or 2 scientific reviewers, a biostatistician, a research subject advocate, and other content experts. The protocol is presented to the full committee (approximately 40 members across a wide range of disciplines and includes junior, mid-career, and senior faculty) for discussion and approval, disapproval or deferment. The review criteria and scoring system follow the NIH 9-point scale. SARC meets twice monthly (minutes are recorded), ensuring that protocols are reviewed within 3 weeks of submission.

Aim 6.2. Utilize OnCore to monitor protocol-specific benchmarks of success. A major focus in the next award period will be to establish the processes by which OnCore will be used to *monitor indicators of the success and fidelity of a protocol*. The specific indicators will be determined, but will likely include: **1)** real-time tracking of enrollment and evaluation of actual vs projected accrual rate; **2)** indicators of adherence (e.g., pill counts); **3)** automated logging of some protocol deviations, such as visits occurring outside the visit window; **4)** manual logging of other protocol deviations; **5)** tracking of adverse events, and **6)** use of OnCore data exports for completion of IRB continuing review applications. Although COMIRB reviews participant enrollment, protocol deviations, and adverse events as part of the continuing review of a protocol, they do not have resources to work with research teams that are not achieving high standards of safety, fidelity, and success. The CCTSI will provide this support in 2 ways: **1)** The Clinical Research Support Center will conduct random audits of ongoing protocols. The goal is to evaluate regulatory compliance, protocol compliance, and best practices. Investigators are provided a written report of status and recommendations for improvement; and **2)** the Study Monitoring Committee (**SMC**) will provide independent monitoring of study safety and integrity for all research conducted in the CTRC Network. The SMC reviews and approves the Data and Safety Monitoring Plan to ensure appropriate safety oversight and conformity with NIH guidelines, and conducts annual reviews of recruitment and adverse events. When problems arise, the SMC Chair meets with the PI to develop remediation plans. The SMC is chaired by Barbara Hammack, PhD, the Research Subject Advocate for the CCTSI since 2008; members include 2 physician scientists, a research pharmacist, and a biostatistician. The SMC meets in person monthly and by e-mail as needed when concerns arise that require prompt attention.

All protocols that meet the NIH definition of a clinical trial are required to be registered at ClinicalTrials.gov. The Clinical Research Support Center educates all research teams on campus of reporting requirements of ClinicalTrials.gov and works with investigators to remain compliant (**see Component E. RKS**). We are developing an automated process by which ClinicalTrials.gov will be used as a complementary approach to track the dissemination of results of CCTSI-supported research.

E. STRUCTURE, GOVERNANCE AND INTEGRATION
Each unit of the PCI (CTRC Network**, Figure 3**) is under the leadership of a Medical Director and Nurse Manager. Dr. Wendy Kohrt (see Biosketch) will oversee the Network and represent PCI on the CCTSI Executive Committee. The CTRC Network will work closely with CRAO, the Regulatory Knowledge and Support and TIN Liaison team to ensure that research involving human subjects is held to high standards of merit, quality, and safety.

Figure 3



F. TIMELINE AND EVALUATION All of the PCI Aims will be launched in year 1 and continued. For Aim 4, it is planned that OnCore will be system-wide by yr 3. Common Metrics developed by the CTSA Consortium and additional local metrics developed by the Evaluation Core will be adopted, collected and reported for evaluation.

COMPONENT F: HUB CAPACITY

REFERENCES CITED

1. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA 297:1233-40, 2007. PMID: 17374817

COMPONENT G: NETWORK CAPACITY

PROJECT SUMMARY/ABSTRACT

Network Capacity: The CCTSI will develop a CTSA **Trial Innovation Network Hub Liaison Team** to closely coordinate with the national NCATS Trial Innovation Centers (TICs) and Recruitment Innovation Centers (RICs) within the Trial Innovation Network (TIN). Providing the foundation for this network expansion, the CCTSI has already played a key role in the many local initiatives to enable the institution's full and robust involvement in the TIN (e.g., ACTA and SMART IRB sign-ons). The Clinical Research Administration Office (CRAO) was created in January of 2016 to bring together in one location the administrative, contracting and regulatory components for clinical trials from across the Anschutz Medical Campus, essential for expansion of our network capacity. This office is well connected to the IRB, the Office of Grants and Contracts, research compliance and other critical institutional bodies necessary to support clinical research, as well as the CCTSI BERD and Informatics Cores. The Hub Liaison Team will build on this centralized research effort to facilitate multi-center trials from the TIN at our center. CRAO also positions the institution to better monitor progress of clinical trial development, start-up, implementation and close-out and to advance efficiencies into these processes. The CCTSI-supported Study Monitoring Committee complements these efforts by providing oversight over ongoing studies and will work with the Hub Team to maintain appropriate levels of accrual support for TIN multi-center trials. In addition, our robust CCTSI clinical research unit network (CTRCs) provides the facilities and personnel needed to conduct these trials. The establishment of the Hub Liaison Team will now provide a local resource to greatly facilitate the performance of NIH-funded (and other) multi-site trials at our institutions through 3 Specific Aims: **Aim 1** will fully establish and optimize the TIN Hub Liaison Team within the CCTSI, developing the infrastructure and personnel to provide ongoing support to TIN studies and local development of multi-site clinical trials. **Aim 2:** The TIN Hub Liaison Team will develop the processes and procedures to adequately facilitate the operationalizing of multi-center trials within the CCTSI, which originate at other sites within the TIN. **Aim 3**: The Hub Liaison Team will support the development and advancement of locally-generated multi-site clinical trials to the TIN. The CRAO provides the foundation that the TIN Hub Liaison Team will build upon, ensuring access to a well-coordinated institutional clinical research administration. The Hub Team will connect and support local investigators in coordination with the TIN resources in this context, allowing for the facilitation of multi-center clinical trials, thus expanding our network capacity.

COMPONENT G: NETWORK CAPACITY

SPECIFIC AIMS

The CCTSI will create a CTSA **Trial Innovation Network (TIN) Hub Liaison Team** in the next grant cycle to develop, support and promote multi-center investigations at our Hub and to provide an environment where clinical trials are conducted efficiently, compliantly and with the highest quality. This will build on the strong research infrastructure within the CCTSI which is currently in place to support clinical trials and will expand the opportunities for our investigators to both propose multi-center trials through the TIN and recruit patients locally for TIN-sponsored trials. The University of Colorado Denver (CU-D) and the UCHealth system have recently completed a physical co-localization of their respective research regulatory, trial budgeting and contracting operations in a joint Clinical Research Administration Office (CRAO). This, along with existing similar integration of research resources at Children's Hospital Colorado (CHCO) and other CCTSI clinical affiliate sites, will provide a strong foundation for the CCTSI's TIN Program Hub which will work with the Trial Innovation Centers (TICs) and Recruitment Innovation Centers (RICs). The goals to expand our Network Capacity will be achieved through the following **Specific Aims:**

Aim 1: Continue to develop and optimize the Trial Innovation Network Hub Liaison Team (TINHLT) within the CCTSI to develop the infrastructure and provide ongoing support to TIN studies and other research activities.

This team will include a TIN Director, Medical Director for both adult and child health, Project Manager, Central IRB Liaison, Contracting Liaison, Recruitment Facilitator, and Research Navigator specifically associated with the TIN hub. The team will include expertise in contracting and will utilize master agreements (ACTA) and single/central IRBs (SMART IRB) between CU-D and the TIN in order to facilitate rapid trial start-up and to interface with the TIN/TICs/RICs. This group will coordinate the TIN with other key CCTSI resources in Workforce Development and Communication to promote the activities of the TIN to the Colorado research community.

Aim 2: The TIN Hub Liaison Team will facilitate the operationalizing of multi-center trials, which originate in other sites of the TIN, within the CCTSI

The TINHLT will identify local Investigators for TIN multi-site trials in both adult and child health and support the trials' local approval, recruitment, start-up and conduct. The Hub Liaison team will interface with the TIN, the RICs and the Accrual in Clinical Trials (ACT) program to perform study feasibility assessments and maximize recruitment potential, particularly those of underserved populations. This engagement will eventually occur at all CCTSI clinical sites to offer an opportunity for broad and systemic engagement.

Aim 3: The TIN Hub Liaison Team will support the advancement of locally-generated multi-site clinical trials.

The local Hub Liaison team and other CCTSI resources will assist investigators with the development of CCTSI-generated proposals to be submitted to the TIN. The Hub team will both educate and communicate with local investigators about the opportunities to open multi-center trials through the TIN and also serve as the local liaison team to assist CCTSI investigators in developing the study and interfacing with the broader TIN resources available.

Common Abbreviations used in this Component

ACTA	Accelerated Clinical Trial Agreement	CTRC	Clinical & Translational Research Centers	PDW	Protocol Development Workshops
ACT	Accrual in Clinical Trials	CE&R	Community Engagement core Resources	SARC	Scientific Advisory and Review Committee
AMC	Anschutz Medical Campus	CU-Medicine	University of Colorado Medicine	SMC	Study Monitoring Committee
BERD	Biostatistics, Epidemiology, & Research Design	DH	Denver Health	TINHLT	Trial Innovation Network Hub Liaison Team
CHCO	Children's Hospital Colorado	DVAMC	Denver VA Medical Center	CU-D	University of Colorado - Denver
CTMS	Clinical trials management system	NJH	National Jewish Health	UCH	University of Colorado Hospital
CRAO	Clinical Research Administration Office	OGC	Office of Grants and Contracts		

COMPONENT G: NETWORK CAPACITY

RESEARCH STRATEGY

A. SIGNIFICANCE

To facilitate and accelerate clinical research at CU-AMC and the CCTSI affiliate hospitals, CU-D has developed centralized infrastructure to provide study design, regulatory and contracting support and integrated systems to assist researchers to more effectively obtain study approval and start-up. Such initiatives, in combination with additional allocation of resources to key offices such as the IRB and the Office of Grants and Contracts (OGC), has resulted in a *50% decrease in clinical trial start-up time over the last 5 years*. However, the focus has been concentrated on single-site, investigator-initiated local protocols. There is a need to expand this support structure to better facilitate multi-site studies led by local PI's or studies originating elsewhere in which our site is chosen as an enrollment site. The development by NCATS of the **Trial Innovation Network (TIN)** provides us with the unique opportunity to collaborate with the Trial Innovation Centers (TICs) and Recruitment Innovation Centers (RICs) to accelerate our participation in multi-site trials. Our new TIN Hub Liaison Team within the CCTSI will enable CU-D to maximize its utilization of these key resources and ensure that local processes are effectively integrated to support these multi-site trials. Furthermore, we will develop and adopt from the RICs a broad range of tools to facilitate recruitment and retention in clinical trials, advancing us from the current state of leaving the responsibility for recruitment to each individual research team with little centralized support to a new model with our Hub Liaison Team providing new tools and mechanisms to enhance recruitment, including honest broker recruitment and patient research registration, as detailed below. These innovations in our ability to conduct multi-site trials align seamlessly with our **Study One-Stop Support (SOS)** concept for supporting all clinical research & trials at CU-AMC and our affiliates (details in **Component A. Admin. Core, Quality and Efficiency**).

B. INNOVATION

B.1. Establishment of CRAO: In 2016, CU-D transformed and centralized our campus clinical research support infrastructure by designing and constructing a new space to house the re-engineered consolidated Clinical Research Administration Office (CRAO). The new integrated shared space is open-concept, "Google style" to facilitate frequent interaction, communication and dynamic problem solving. The teams moved into this new space in early January 2016 and it has greatly enhanced communication, efficiency, problem solving and streamlining our processes. There are currently 15.5 FTE co-located in this integrated space who are responsible for the clinical research services outlined in **Table 1.**

Table 1. Research Services of CRAO

Pre-Approval Process	Operations	Post-Approval
Portal submission	Contracting	Research billing
Affiliate review	Contract facilitators	Recruitment assistance
Scientific review of protocols	MTA facilitators	CTMS reports
Budget negotiation	Central IRB facilitator	Clinicaltrials.gov data entry
Feasibility assessment	Regulatory facilitator	Facilitate data sharing
Coverage analysis	CTMS calendar and budget builder	Study monitoring
Pricing	CTMS training	Regulatory audits
Facilitation		Training support
FDA submissions		Study close-out and evaluation
Clinicaltrails.gov registration		

B.2. Clinical trials management system (CTMS) expansion with affiliates: Historically, the CU-AMC and CCTSI affiliates have had a fragmented and decentralized approach to clinical research management with little visibility to anyone but the individual study team who were actually running the clinical trial. As outlined below, CU-AMC in collaboration with UCHealth is in the process of transforming this paradigm, by implementing a CTMS (OnCore) that will provide the backbone infrastructure for clinical trials across CU-D and the UCHealth system. *Negotiations are also on-going with CHCO, DH and DVAMC to use the same CTMS system*. If it is possible to integrate systems, this will create an unprecedented opportunity to use a single management system across the CCTSI affiliate sites to facilitate clinical research and trials. Such an integrated system will provide easy access to Common Metrics, enable proactive support for recruitment, and allow supporting institutions to better understand how investing in clinical and translational research aligns with their clinical mission.

B.3. Integration with Community Engagement & Research (CE&R) Core Resources: Clinical research-related materials to be accessed by the public need to be community sensitive. We propose the addition of a new Research Educator position that will interface with the CE&R core, and specifically with Community Research Liaisons, to broaden community interest and knowledge about participation in research. Our CCTSI Evaluation Core will monitor the effectiveness of this program and its integration with the TIN Hub liaison team.

B.4. Education of the workforce to understand role and responsibilities relating to use of a central IRB and the TIN resource: Current training programs are being updated and will emphasize differences between using a local and a central IRB. The TIN Hub Liaison Team will work with the TICs and our local clinical research education program to further develop, implement, and disseminate such education and informational materials.

B.5. Study Monitoring Committee (SMC) Oversight expansion: The CCTSI successfully monitored ongoing Clinical & Translational Research Center (CTRC) studies for the past 5 years and intervened to assist failing studies. The ability to use the new CTMS to monitor progress of studies (e.g., recruitment and retention) will greatly enhance the ability of the Recruitment Liaison to work with the SMC (which reviews progress of ongoing clinical studies and trials) to develop early identification and intervention for potentially failing studies embedded in the TIN.

C. PRELIMINARY DATA / INSTITUTIONAL ASSETS

The following mature infrastructure in place at CU-D and its affiliates will be expanded, enhanced and leveraged by the Trial Innovation Network Hub Liaison Team to accelerate our ability to conduct multi-site trials:

C.1. The Colorado Multiple Institutional Review Board (COMIRB): Transformational efforts at creating a local central IRB have been ongoing in Colorado since COMIRB was established in 1991 as the sole IRB of record for the following CCTSI affiliated organizations: CU-D, Anschutz Medical Campus (AMC), CHCO, DVAMC, DH, and University of Colorado Hospital (UCH). Through a formal affiliation agreement between each of these hospitals with CU-D, a researcher can get approval for at least 5 sites via one COMIRB submission. This approach set a historical precedent and remains a model nationally. COMIRB approved a large number of clinical trials in the first 6 months of 2016, with excellent start-up times for multi-site trials (**Table 2**).

C.2. Use of External IRBs: In an effort to streamline the workflow, in January 2016 CU-D developed a new process for vetting requests to rely on external IRBs and their institutions. This process provides a mechanism to ensure effective communication and timely review by other institutional and/or regulatory committees, such as privacy, conflict of interest and the hospital affiliate approvals.

C.3. Office of Grants and Contracts*:* OGC at the CU-D, a centralized sponsored program administration unit that reports to the Vice Chancellor for Research, adjudicates grant proposals/awards, negotiates contracts (other than clinical trials) and subcontracts, establishes awards in the university's financial systems, and performs compliance oversight for those awards. Clinical trial contracts are negotiated and managed by CRAO.

C.4. A single portal for pre-IRB submission of research protocols to hospitals (CHCO and UCH) as well as all the CTRC units was established in August 2014. This project removed barriers and created a unified process for human subject research protocol submission. The portal provides a single entry point into the pre-IRB review process to enable the institutions to evaluate the budget and feasibility of protocols while also reducing redundancy and improving efficiency. Each institution has committed to additional IT system integrations to further reduce duplication by using the OnCore CTMS.

C.5. The CCTSI Scientific Advisory and Review Committee (SARC): SARC has expanded its mandate and now serves as the scientific review committee for the *entire AMC* in addition to the CTRC units as of August 4, 2014. All protocols that meet the NIH definition of a clinical trial that have not undergone external peer review for scientific merit, are now reviewed by SARC. In 2016, SARC reviewed 103 CTRC protocols, 62 at full board and 32 non-CTRC protocols with 36 studies currently pending and 5 withdrawals. To augment SARC review, there is also a CCTSI Research Ethics Consult Service to address a broad range of activities such as informed consent questions and the communication of concerning results from an anonymous survey.

Table 2. Studies approved by the IRB between 1/1/2016 and 6/30/2016* - Data shown are mean calendar days

	Contract/sub-contract Received to Execution	Contract executed to Enrollment of 1st Subject	IRB Submis-sion to Approval	IRB Approval to 1st Subject Enrolled
Phase III Multisite	82	48	21	71
Other Multisite	95	45	15	67
Single Site	116	67	39	82

An electronic CTMS (OnCore): purchased jointly by CU-D and UCHealth, is configured to provide significant backbone infrastructure to support the conduct of clinical trials. The system will eventually be available to all researchers conducting any human subject research within CU-D or UCHealth and serves as a document manager, a data collection tool, a tracker of subject participation to the protocol calendar and financial management system. The

biospecimen module is also live. There are 62 biospecimen projects currently in the system with the plan to put all future biorepository data in the system, and integrate it with Health Data Compass, our research data warehouse.

D. APPROACH

Aim 1: Continue to develop and optimize the Trial Innovation Network Hub Liaison Team (TINHLT) within the CCTSI to develop the infrastructure and provide ongoing support to TIN studies and other research activities.

Currently most CCTSI resources have focused on improving clinical trial start-up times and supporting locally developed single-site studies. The addition of the CTSA TIN will expand our multi-site portfolio and provide important resources for local investigators who want to serve as the lead PI on multi-site, national studies. The TIN liaisons will be integrated within the CRAO and CCTSI to provide a single point of entry of all clinical research support and structure related to multi-site trial proposals. Staff will make these resources available not just to the campus but also to the CCTSI affiliate or partner hospitals where the research is conducted.

Table 3. Trial Innovation Network Hub Liaison Team (TINHLT)

Name	Institution	Position/Department	TIN Hub Team Role & Responsibilities
Thomas Flaig, MD	CU-D UCHealth	Associate Dean/Chief Clinical Research Officer, UCHealth	**Director** - Responsible for overall operations of the TIN, participation in conference calls and meetings, and communications with TICs and RICs and NCATS
Thomas Campbell, MD	CU-D	Professor, Medical Director UCH CTRC	**Adult Medical Director** - Responsible for operations and implementation of adult clinical trials of the TIN
Peter Mourani, MD	CU-D CHCO	Associate Professor. Medical Director, CCRO at CHCO	**Child Medical Director** - Responsible for operations and implementation of child health clinical trials of the TIN.
Benjamin Echalier, MS, MBA, CCRP	CU-D	CCTSI Clinical Research Operations Manager	**TIN Project Manager** - Responsible for project management, oversight and implementation of TIN protocols at our site.
Christy Williamson, CCRP	CU-D	CRAO Senior Facilitation Manager	**Central IRB Liaison** – Responsible to ensure timely and compliant IRB reliance agreements, facilitate use of central IRBs, and streamline local IRB processes.
Amanda Peng, MS	CU-D	CRAO Senior Clinical Trial Contracts Manager	**Contracting Liaison** – Responsible to facilitate timely and complete execution of contracts related to the TIN.
Barbara Hammack PhD	CU-D	CCTSI Research Subject Advocate	**Recruitment Facilitator** – Responsible to develop, implement and facilitate research participant recruitment & retention with RICs.
Cynthia Sneddon, MPH, CCRC	CU-D	CRAO Regulatory Facilitator	**Research Navigator** – Responsible to assist investigators in the front-line in accessing the resources of the TIN, RICs, TICs and CCTSI.
TBA			**Honest Broker for Recruitment** – New position responsible for subject identification working closely with Healthdata Compass.

Aim 1.1 Develop the TIN Hub Liaison Team

Approach 1: TIN Hub Liaison Team Establishment: To facilitate the operationalization of the TIN within the CCTSI, a local Hub team is being assembled that brings together key personnel with extensive knowledge and experience relating to CCTSI resources, research administration, clinical trial operations, regulatory issues and grants and contracts. This talented team (**Table 3; details in Biosketches and Facilities and Other Resources**) will serve as liaisons between local investigators and the TIN, TICs and RICs and assist with local implementation. It will meet as a group at least monthly and participate within the national TIN program. Our BERD, Informatics and RKS cores will also assist investigators in study design.

Approach 2: Integration with CRAO. To avoid developing a parallel structure for TIN clinical trial development and implementation at CU-D, the TIN liaisons will be imbedded in the CRAO office space and work closely with the CRAO team. The TIN Hub Liaison Team will establish the regulatory and legal structure needed to implement TIN trials within the CCTSI and its CTRC facilities. The Hub team will use their expertise and local contacts in many cases to effectively operationalize and optimize these efforts.

Approach 3. Develop a communication plan to disseminate information locally. The Evaluation Core Needs Assessment Survey in 2016 indicated that the current clinical research resources on campus are not universally known. Thus, the TIN Hub Liaison Team will work closely with our CCTSI Communications Director, Wendy Meyer, who will coordinate with communication experts on campus and at the hospital affiliates to create broader awareness of the TIN. CHCO and UCHealth are also in the process of developing broader research communication campaigns including multi media advertising, updated clinical research web presences, brochures, flyers, videos on the importance of clinical research and why it is important for patients and the public

to be involved. Clinicaltrials.gov and the CU-D integrated research webpage will be used to provide current and accurate information to potential participants, researchers and clinicians and providers in the community. UCHealth and CHCO are further working to integrate this information with their EHRs to provide real-time alerts for treating physicians (**see Overall Component for more details**). The CCTSI Communication Plan will:

- Develop materials and local TIN website pages, engage communications experts, collaborate with CE&R Core, and the establish the Research Educator position
- Utilize existing e-communication, meetings and individual outreach mechanisms already in place
- Educate investigators and their research teams about the TIN
- Establish a method to match local investigators with national TIN trials and evaluate its effectiveness

Aim 1.2. Develop Master Agreements: CU-AMC signed on to the ACTA agreement in 2015. We now offer the ACTA as a starting point with industry sponsors if they are willing to accept minor revisions to the Indemnification Section to meet the requirements of Colorado State Law, specifically the Colorado Government Immunity Act. We are actively working with the national ACTA team to develop language to address this issue. Otherwise, we are currently using ACTA either as our template language for the initial redline or as our back-up language. Since this change was only recently enacted in 2016-17, we do not yet have data to demonstrate a further decrease in the time to negotiate contracts, however we are collecting these metrics.

Aim 1.3. SMART IRB and use of Single/Central IRBs: CU-AMC signed on to SMART IRB in February 2017. As detailed above, the CU-D campus is using a single web portal for study protocol submission, which will enable our Hub Liaison team to identify in a timely manner if an agreement already exists with a central IRB or if a new relationship needs to be established. The Liaison team will work closely with the TICs (if the TIC becomes the new central IRB) or with our own external IRB coordinators in CRAO if an IRB reliance agreement needs to be developed and executed with another external IRB. **Our Institutions are fully committed to work with the TIN and NCATS to utilize central IRBs for all TIN studies** (**see Letters of Support, Overall Component**).

Aim 2: The TIN Hub Liaison Team will facilitate the operationalizing of multi-center trials, which originate in other sites of the TIN, within the CCTSI.

The CCTSI Hub Liaison team will identify local Investigators for both adult and child health proposed TIN trials and support the trials' local approval, start-up and implementation. This engagement will occur at all CCTSI clinical sites over time to offer an opportunity for broad engagement.

Aim 2.1. Identification of Local PIs for TIN multisite studies: In preparation for TIN trials that originate from other sites, the TINHLT Director, in collaboration with the two Medical Directors and the TIN Liaison Team, will develop a list of primary researcher contacts for the 25 most active clinical research/trial groups at UCH and CHCO, who will be charged with matching a local PI with the appropriate expertise for proposed TIN supported multi-site studies that do not originate from our site. For other proposed TIN trials that don't involve these research groups, the Director and Medical Directors will use local search tools (e.g., Colorado PROFILES, prior OGC contracts) and direct contact with Division/Center directors to identify potential local PIs. Our TIN Hub Liaison Team will then provide the PI with information about the trial and assurance that regulatory, contracting and implementation support will be provided by the Team and the CTRCs.

Aim 2.2. Feasibility assessment: Assessment will be performed within the Health Data Compass (as **detailed in Component B. Informatics**). Researchers at AMC will have access to CU-AMC, CHCO, and UCHealth patients' de-identified information using our i2b2 platform, which has been made more user-friendly with remote desktop accessibility by incorporating a TriNetX web interface. All proposed TIN studies will be required to have conducted such a feasibility assessment. The RIC Liaison will conduct this assessment for TIN multi-site studies that use the CCTSI as a local site. For multi-site studies originating from a CCTSI investigator, the Accrual in Clinical Trials (ACT) mechanism using i2b2/SHRINE will be utilized to search for cohort numbers at other CTSA Hubs in the study planning process, through the UPMC/Harvard mechanism in which we are active participants (**see Component B. Informatics**). Other TIN mechanisms for cohort identification to be developed nationally will be implemented at our site through our Translational Informatics Core.

Aim 2.3. Recruitment of Potential Research Participants.

Approach 1. Honest Broker using Health Data Compass at UCH: CU-AMC, CHCO, UCHealth, and CU-Medicine together have developed Health Data Compass, an integrated data warehouse, which includes medical record and financial data for pediatric as well as adult patients. Currently, only researchers who have a treatment relationship with patients can access recruitment information to contact potentially eligible subjects. A trained Honest Broker, endorsed by each of the key parties including COMIRB, will be hired and trained to work with

research groups who need broader access to recruitment populations in which making a treatment relationship is impractical (e.g. patients with asthma, diabetes, chronic pain). Contact information will be made available to the Honest Broker for IRB approved recruitment. The Honest Broker will make initial contact and if the patient is interested in the trial, then provide the research team with the contact information to initiate the consent process. This mechanism for recruitment will be carefully monitored, tracked and evaluated by our Evaluation Core and CRAO.

Approach 2. Recruitment Initiatives at Children's Hospital Colorado: CHCO is in the process of building a research participant database (permission to contact about research studies), which will primarily be fed by an "opt in" process when patients are being registered at CHCO. In addition, recruitment of patients outside of those having treatment relationships with CHCO will be accomplished through marketing campaigns being conducted in the Denver metro area and by the creation of a research participant database portal on the CHCO external website where parents will have the opportunity to join their children in the database.

Approach 3. Additional Recruitment Plans. Community Research Liaisons: The CE&R Program has been a key partner for building community/academic research relationships. We will work closely with the RCLs to broaden the reach of recruitment in a community-engaged and culturally-sensitive manner.

Approach 4. TrialSpark recruitment tool: The CCTSI will pilot this e-based tool, which uses social media for recruitment, in order to better understand its effectiveness to recruit difficult to reach populations. We are currently working with 3 beta testing protocols to conduct an evaluation and return on investment analysis in collaboration with the Evaluation Core. If it is promising based on this evaluation, we will develop a subsidized fee-for-service model with TrialSpark to serve as an additional resource for recruitment.

Approach 5. Recruitment Approach Comparison: As outlined above**,** UCHealth is proceeding with an Honest broker recruitment approach and CHCO is using a research participant database approach. These 2 different approaches may best fit each institutional needs and resources, but will also offer us an opportunity to compare the effectiveness of the approaches. In collaboration with RKS and Evaluation Cores, we will collect and analyze defined metrics for both approaches including time to startup/initiation, number of trials using, number of subjects identified, costs, sustainability, etc. If one clear best approach emerges, its adoption would be pursued more broadly and our analysis and recommendations would be disseminated to other CTSA hubs.

Approach 6: Investigational drug management - Investigational Product Review Committee (IPRC): Implemented in May of 2016 to review protocols in which a CU-D faculty member plans to initiate a human trial with an investigational product (drugs, biologics, devices, supplements, etc.), the IPRC is a collaboration between CU-AMC, CHCO and UCHealth to review these studies to assure there is an appropriate plan in place. All TIN trials will undergo this local review and be provided assistance if needed by the TINHLT. In addition, the Skaggs School of Pharmacy and Pharmaceutical Sciences in collaboration with the SOM and CCTSI will develop a fee-for-service compounding resource for trials, and will train pharmacy students about the specific regulatory requirements relating to research pharmacy, to help build research teams for the future.

Aim 3: The TINHLT will support the advancement of locally-generated multi-site clinical trials.
The CCTSI Hub team will both educate and communicate with local investigators about the opportunity to open multi-center trials through the TIN and serve as the local liaison to assist CCTSI investigators in study design and interfacing with the broader TIN resources available.

Aim 3.1. Local Investigator Assistance Program: We will develop a new support structure to assist local PI's who plan to develop multi-institutional clinical trials, aligned with our Study One-Stop Support (SOS) concept. We will assist in ensuring that all TIN clinical trial proposals are developed to a mature enough state before accessing TIC/RIC/TIN resources. In addition, we will implement a communication plan (emails to CCTSI Members, town hall meetings, e-newsletter stories, etc.) to inform local investigators about this new and exciting opportunity. Under the direction of Tom Flaig, who has set up the existing successful protocol development core in the CU Cancer Center, we will use the expanded BERD and RKS *Study Jump-Start Consults* with a team of local expert clinical trialists who will be available to guide and mentor investigators in the development of the scientific and statistical basis, operations and procedures for multi-site protocols. A protocol template will be built using the existing Cancer Center clinical trial template as its foundation. Coordinated by our local TIN Project Manager, appropriate CCTSI Hub Liaison Team members will assist with early development of budgets, contract templates, consent forms, potential IRB issues, operational details, etc. Our Recruitment Facilitator and Informatics Core will work with the investigator to assess the feasibility of the study and determine which other CTSA sites will have adequate sized cohorts by using i2b2/SHRINE or other feasibility assessment tools to be

developed by the RICs/TIN. Additional local resources and expertise will also be available to ensure ethical, compliant, scientifically rigorous multi-site protocols are developed and then ready for submission to the TIN/TIC/RIC portal for review. Once developed, a TIN local project manager and a Community Research Liaison will be assigned to each multi-site study to facilitate the TIN/TIC/RIC submission and approval process, assist with any regulatory or operational issues that may then develop, and key resources for the study team over the lifespan of the study.

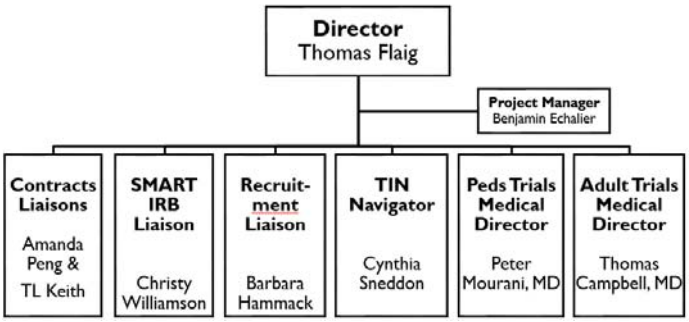
The extent to which the proposed multi-site trial will request national TIN/TIC/RIC resources vs. using local resources will be determined early in the protocol development. If local resources are to be utilized, the TIN Hub Liaison Team will work with the local PI to implement the approved monitoring and audit plan. Such studies will also be subject to remote monitoring/auditing by CRAO as such processes are developed using the CTMS.

Aim 3.2. Mechanisms for Protocol Development:

Approach 1: Protocol Development Workshops (PDW): The PDW is a new resource on the AMC, established during the current grant cycle, which will be modified to play a key role in cultivating locally generated multi-center clinical trial proposals. This novel class concept is designed to instruct in key concepts of scientific design and human research protocol writing, while learners complete a submission-ready protocol. This series of six hands-on sessions, limited to small groups, emphasizes facilitated learner interaction and critique, supported by didactic discussions and written self-directed guides. Critical skills taught through the sessions include sound study design with adequate scientific control, selecting optimal outcome measures, data analysis, thought organization, scientific writing for protocols, and oral presentation. The PDW was intended for Junior Faculty, Fellows, and Residents of all disciplines pursuing a mentored research project but will be expanded as a resource to assist any investigator in developing a clinical trial protocol. The Workshop was launched in March 2016 and is offered 4 times per year; as of December 2016, 20 learners (1 Resident, 5 Fellows, 2 Instructors, 11 Asst. Professors, and 1 Professor) have participated, spanning pediatric and internal medicine subspecialties, neurology, psychiatry, radiology, college of nursing, school of pharmacy, and physical therapy.

Approach 2: Research Studio Program: The CCTSI also supports the Research Studio program (directed by Jane Reusch MD) for assistance with protocol development. The Studio format includes 90-minute consultative panels of 3-5 carefully selected local experts from varied disciplines. After a brief presentation from the investigator, there is a focused discussion around the key areas for success of the project. Within the Studio's T1-2 translational support, the development of multi-centered clinical trials aligns with the objectives of this program.

E. STRUCTURE, GOVERNANCE AND INTEGRATION



The TIN Hub Liaison Team structure (**Figure**) is outlined in Aim 1 and Table 3 (**see Facilities & Other Resources for further details**). Our TIN efforts will initially be concentrated at the CU-AMC campus, but will also be available for assistance with protocol development and participant enrollment to investigators across the CCTSI affiliate sites. Thomas Flaig, MD, the TIN director, who as the UCHealth CCRO has authority and responsibility for clinical trials conducted at non-AMC UCHealth sites, is ideally situated to expand TIN studies across UCHealth. Also ensuring success for our TIN Liaison Team efforts is the close working relationship of Tom Flaig, Alison Lakin, Associate VC for Regulatory Compliance, Ronald Sokol (PI) and Tim Lockie, Admin Director of the CCTSI. To coordinate integration of trials into the workflow of the CTRC units, adult and child health CTRC medical directors are in the Hub Liaison Team. In addition, as we expand to other affiliate sties, an operational coordinator will be identified at each of the CCTSI affiliate site to ensure appropriate integration across the CCTSI

F. TIMELINE AND METRICS / EVALUATION

All 3 Specific Aims will be developed in 2017 and will be mature enough for implementation in Year 1 of the new funding cycle. As the CTSA Consortium and the TIN develop Common Metrics for Network Capacity, we will implement collecting, tracking and reporting them through our Evaluation Core and the TIN Hub Liaison Team. We will also develop local metrics, in conjunction with our Evaluation Core, that we will track and evaluate for continuous quality improvement. Examples of such local metrics may include the number of local protocols under development for multi-site implantation, number of multi-site TIN protocols that we have implemented at our site and our enrollment in those protocols, time for study start-up for TIN trials, satisfaction of research teams, etc.

COMPONENT H1: EARLY LIFE EXPOSURES PROGRAM

PROJECT SUMMARY/ABSTRACT

The overall goal of our **Early Life Exposures Program (ELEP)** Optional Component is to enable investigators in diverse disciplines and all career stages to train, participate, and excel in research focusing on human health and diseases that have their origins at early stages of life. As a result, the ELEP will foster a new generation of scientists trained in the complexities of translational research involving pregnant women and their offspring from infancy through childhood and adolescence. The premise of our ELEP is that pre-emption of diseases and prevention of their later life consequences will improve health and quality of life by reducing disease burden and its devastating economic impact on individuals and society. Thus ELEP will align with the CTSA Lifespan Domain Task Force through objectives focused on early life exposures. Within the CCTSI framework, the ELEP will integrate a large number of existing and well-funded research programs in maternal-placental-fetal and pediatric medicine, each with multiple investigators and trainees. The ELEP will support new multidisciplinary collaborations among basic/pre-clinical, clinical, and translational scientists at the University of Colorado Anschutz Medical Campus (CU-AMC) and in the CCTSI community. The ELEP will provide research and training infrastructure to facilitate early life exposures research and longitudinal lifespan/life course research. The ELEP will provide an innovative platform for prospective, observational and experimental approaches as a national model for CTSA centers engaged in lifespan research in order to promote collaborations among CTSA hubs. These goals will be achieved by the following Specific Aims: **Aim 1**: Expand and streamline our broad-based, multidisciplinary organizational structure to promote Early Life Exposures clinical-translational research in the CCTSI. **Aim 2:** Provide coordinated research support and development. **Aim 3**: Foster new education and training opportunities in Early Life Exposures research. By implementing these aims over the next 5 years, we will enhance the ability of our numerous outstanding scientists and team-based research programs, and attract and train new investigators, in child-maternal health research to have a significant and sustained impact on human health and development, with the ultimate goal of translating discoveries into interventional studies and clinical trials very early in life with high potential to improve quality of life across the lifespan.

COMPONENT H1: EARLY LIFE EXPOSURES PROGRAM

SPECIFIC AIMS

The overall goal of our Early Life Exposures Program (ELEP) is to enable investigators in diverse disciplines and all career stages to train, participate, and excel in research focusing on human health and diseases that have their origins at early stages of life. As a result, the ELEP will foster a new generation of scientists trained in the complexities of translational research involving pregnant women and their offspring from infancy through childhood and adolescence. The ELEP will align with the CTSA Lifespan Domain Task Force through objectives focused on early life exposures. Within the CCTSI framework, the ELEP will integrate and connect a large number of existing and well-funded research programs in maternal-placental-fetal and pediatric medicine, each with multiple investigators and trainees. The ELEP will support new multidisciplinary collaborations among basic, clinical, and translational scientists at the University of Colorado Anschutz Medical Campus (CU-AMC) and in the CCTSI community. The ELEP provides research and training infrastructure to facilitate early life exposures research as a fundamental entrée into longitudinal lifespan/life course research. The ELEP also will provide an innovative platform for prospective, observational and experimental approaches as a national model for CTSA centers engaged in lifespan research, aimed at promoting collaborations among CTSA hubs.

Our unique ELEP is based on well-established observations that adaptations to adverse exposures in early life (fetal, neonatal, infancy, early childhood) predict disease risk with onset years to decades later. Mounting epidemiological evidence supports the novel concept that diseases as diverse as autism, obesity, diabetes, schizophrenia, cancer, hypertension, asthma, myocardial infarction, and Alzheimer's have their origins—at least in part—in exposure to an adverse intrauterine environment.[1] Because of the temporal separation between cause and effect across the lifespan, mechanistic and interventional research is challenging in humans. Our premise is that primary prevention strategies early in development, including during pregnancy and early infancy, are likely safer, more effective, and less costly than interventions later in life,[2] and will ultimately improve health and quality of life by reducing disease burden and its devastating economic impact on individuals and society. Our numerous outstanding scientists and team-based research programs in child-maternal health research at CU-AMC will create the nidus for the ELEP, with the ultimate goal of translating discoveries into interventional studies and clinical trials with high potential to improve quality of life across the lifespan. To accomplish the overall goals of our ELEP, we propose three **Specific Aims**:

Aim 1: Expand and streamline our broad-based, multidisciplinary organizational structure to promote Early Life Exposures Clinical-Translational Research in the CCTSI. We plan to develop two complementary groups: 1) the Perinatal Research Network, a campus-wide research infrastructure, and 2) ELEP disease-specific Working Groups to promote collaborative team-based research within the CCTSI and existing CU-AMC programs. These platforms will work synergistically toward establishing collaborative studies among national CTSA networks, particularly the CTSA Lifespan Domain Taskforce (DTF) and its Early Life Exposures (ELE) Working Group and Lifespan Toolkit Group, as well as NIH disease-specific and rare disease networks.

Aim 2: Provide coordinated research support and development. Maximize investigators' capacities to design and conduct *perinatal* clinical-translational research through the Perinatal Clinical Translational Research Center (PCTRC). Ensure participation of all investigators conducting clinical-translational ELE research in the Perinatal Research Facilitation Committee (PRFC), with support from a research advocate/ coordinator. Maximize enrollment of pregnant women and their young children into studies by expanding use of the PerinAtal RegIsTrY (PARITY) as a centralized recruitment database, through support from a skilled database manager.

Aim 3: Foster new education and training opportunities in Early Life Exposures research. Incorporate current child and maternal health research, education, and training programs into an effective translational research training program for ELEP investigators, emphasizing team-based research. Develop approaches for engaging investigators in collaborative research studying populations from diverse racial, ethnic, physical and mental abilities, and socioeconomic backgrounds.

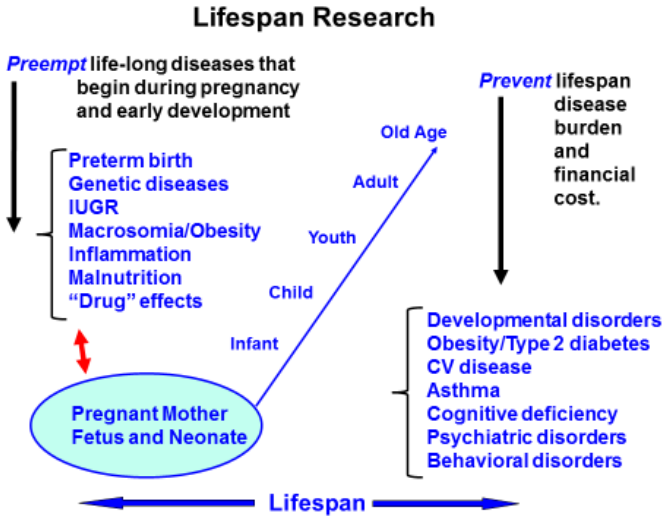
Common Abbreviations used in this Component

BB	Baby Blanket	CHRCD	Child Health Research Career Development	ELEP	Early Life Exposures Research Program
BBB	Building Better Babies	CTSA	Clinical Translational Sciences Award	PARITY	PerinAtal RegIsTrY
CFCC	Colorado Fetal Care Center	CU-AMC	University of Colorado Anschutz Medical Center	PCTRC	Perinatal Clinical Translational Research Center
CMH	Child Maternal Health	DOHaD	Developmental Origins of Health and Disease	PRFC	Perinatal Research Facilitation Committee
CCRO	Children's Clinical Research Organization	CHRCD	Child Health Research Career Development	PND	Perinatal Database
CCTSI	Colorado Clinical and Translational Sciences Institute	DTF	Domain Task Force	PRN	Perinatal Research Network

COMPONENT H1: EARLY LIFE EXPOSURES PROGRAM

RESEARCH STRATEGY

A. SIGNIFICANCE AND PREMISE. The Early Life Exposures Program (ELEP) will promote clinical and translational research (CTR) throughout the CCTSI partner institutions with a focus on the Developmental Origins of Health and Disease paradigm (DOHaD), namely, that adverse influences in early life (fetal life, infancy, childhood) have a profound impact on health and disease throughout the lifespan.[3,4] Because much of chronic disease is programmed during the period of life from conception through early childhood, preemptive interventions, which is a major goal for our program, are likely to have the greatest impact and economic productivity if initiated during these periods.[5] **(Figure).** Based on this premise, our unique ELEP will promote and enhance multidisciplinary, integrated research programs at early stages of life and support investigators who focus on preventive strategies to attenuate diseases with early life origins. **Our ELEP dovetails with the national CTSA Lifespan DTF ELE Working Group and Lifespan Toolkit Group** and their emphases on: 1) integrating translational science during the early stages of life to attain health improvements in the population, 2) studying individual differences in the progress and treatment of disease processes, 3) identifying infrastructure and training needs to conduct effective lifespan research, 4) identifying early life disease processes and gaps in knowledge and scientific approaches to address these, and 5) developing methodology for conducting lifespan research starting with early life exposures. The number of survivors of childhood illness is rising dramatically[6], underscoring the need for research that specifically assesses the impact on adolescents and adults who are living longer with chronic health conditions that originated earlier in their lives.[7] Opportunities to prevent, postpone, or ameliorate the natural history of acute and chronic conditions through early targeted interventions can best be conducted by translational scientists using data from early life exposure studies. This necessitates integrating collaborative databases and biorepositories among clinical scientists who are otherwise focused on specific diseases. Training programs also are critically needed to develop investigators studying periods of developmental plasticity and the effect of early and cumulative exposures on future generations.



B. INNOVATION. The proposed ELEP is distinctive nationally in providing approaches for training and clinical-translational study of diseases that begin early in life and their developmental trajectories that encompass fetal and neonatal periods, infancy, childhood, and adolescence. Focus also is placed on life course events including birth; immune, cardiopulmonary, and metabolic development; school performance (motor, cognitive, social); emotional development and attachment, etc. An essential consideration is the inseparable relationship between the mother/fetus/child such that maternal health and disease have direct, life-long impact on the health of the child and, particularly in female offspring, intergenerational transmission. We developed the innovative ELEP, taking these unique considerations into account, to address the specific complexities of employing an early intervention perspective on human health and development beginning at the earliest stages of life.

B.1. Interactions with the National CTSA Consortium: Our ELEP has two unique strengths that are designed to make substantial contributions to the national CTSA consortium and the national CTSA Lifespan Domain Task Force Early Life Exposure Working Group. 1) We have developed a *novel Early Life Exposures approach* to CTR, emphasizing the fundamental importance of child and maternal health to the prevention of adult disease. 2): Our innovative program provides a model for the CTSA programs to create a national CTSA-Consortium research and training network for child and maternal health, to serve as a basis for development of best practices for ELE research, training, infrastructure, and regulatory processes in the CTSA Consortium and provide links with major national studies (e.g., NIH ECHO program).

B.2. Areas identified by the CCTSI Evaluation Core for innovation in the ELEP: Using member surveys and Q&A sessions with faculty and trainees, the following identified needs are addressed in the current proposal:

- Focus on early life exposures and conditions that portend later life disease.
- Enhance an integrated, multi-disciplinary, longitudinal framework for research of the unique developmental aspects of the maternal-fetal unit, neonate, child, and adolescent.

- Build campus-wide ELE research infrastructure that all researchers can utilize and benefit from. The PRFC maintains a database of all protocols in the prenatal clinics, labor & delivery suites, NICUs, and well-baby nursery and encourages investigators to participate in pre-IRB review, facilitates overlapping research endeavors, and develops common consent forms and SOPs for sample collections. Buy-in from investigators will be promoted by the PRFC and the PCTRC, providing skilled assistance in this special population through study feasibility and design guidance, subject recruitment, sample collection, and *facilitation of collaborations to reduce competition for limited numbers of subjects.*
- Make PRFC pre-IRB review obligatory *to avoid unethical overburdening of subjects with independent and often multiple recruitments (based on recommendation from our External Advisor, James Heubi, MD, Cincinnati).*
- Broaden leadership base to assure collaboration among pediatric, maternal, and adult research programs.
- Integrate programs (training, seminars, mini-symposia, etc.) to facilitate development of collaborative projects among pediatric, obstetric, and adult medicine faculty and trainees.
- Centralize infrastructure for all aspects of ELEP research, providing research support personnel, clinical trials support, streamlined compliance, and shared tissue biorepositories and databases.
- Ensure that ELE research projects are inclusive of subjects from diverse backgrounds of all kinds.

C. PRELIMINARY DATA. Our Institution has produced many investigators who have participated for decades in basic, translational, clinical, and epidemiological ELE scientific investigation. Seminal programs include perinatal (maternal, placental, and fetal physiology), pediatric subspecialties, and collaborations in medical, behavioral, outcomes, and community-based research (Table 1, and References from CU-D Faculty [9-57]*).*

Table 1. University of Colorado Early Life Origins Research Groups

Department or Division	Program
Pediatrics	
Perinatal Research Center, (Hay, Rozance, Brown, Wesolowski, Wright)	Fetal growth and organ development, intrauterine growth restriction and mechanisms underlying DOHAD
Pediatric Gastroenterology and Hepatology (Sokol, Narkewicz, Mack, Furuta, DeZoeten)	Childhood Liver Disease Research Network (ChiLDReN); IBD, celiac disease, eosinophilic GI diseases, liver transplantation, immune-mediated GI diseases
Neonatal nutrition (Hay, Brown, Hendrickson, et al.)	Optimization of neonatal nutrition and postnatal growth
Childhood Nutrition (Krebs, Young, Friedman, et al.)	Nutritional influences on programming & infant growth
Pediatric Heart Lung Center (Abman, Kinsella, Mourani, et al.)	Neonatal persistent pulmonary hypertension—nitric oxide treatment; prevention and treatment of bronchopulmonary dysplasia
Neonatal Outcomes Research (Hwang, et al.)	Epidemiology, health services, post discharge health outcomes
Allergy and Asthma (Atkins, Fleisher, Greenhawt)	Early allergy and asthma; development of the immune system
Colorado Inst. of Maternal-Fetal Health and the CO Fetal Care Center (Crombleholme, Zuk)	Combined UCH-CHCO program for clinical care and research involving high risk pregnancies and fetal development
Infectious Disease (Levin, Simoes, et al.)	Maternal vaccination to protect mother and fetus
Pediatric Endocr. (Nadeau; Green, Zeitler, Rewers,)	Childhood & adolescent metabolic disease; PCOS; diabetes, celiac disease
Child abuse and neglect (Runyan, Krugman)	Kempe Center for Child Abuse and Neglect
Obstetrics and Gynecology	
Maternal Fetal Medicine (Su, Hobbins, Hurt, Metz, Hoffman)	Placental vasculature, IUGR, pre-term birth, maternal mental health, and marijuana use
Reproductive Sciences (Jansson, Moore, Powell)	Placental function; mechanisms of preterm birth; effects of altitude, maternal diet, and obesity on pregnancy outcomes
Repro. Endocrin. (Santoro, Polotsky, Skaznik-Wikiel)	Role of diet and obesity on fertility and reproductive success
Building Better Babies (Jansson, et al.)	Prevention of developmental disorders in pregnancy/early infancy
Medicine	
Colorado Program for Nutrition and Healthy Development (Friedman, Barbour, Hernandez)	Impact of maternal obesity and diet on intrauterine metabolic environment and risk of obesity in the child, including attenuation measures.
NIH Nutr. Obesity Res. Ctr. (Bessesen, et al.)	AMC program, multiple PIs and studies of obesity and nutrition
Psychiatry	
Prenatal origins of psychiatric disorders (Freedman, Hoffman, Law)	Molecular mechanisms for intrauterine development of behavioral disorders; autism, schizophrenia, ADHD, etc.
School of Public Health	State Newborn Screening; Ctr. for Global Child Health Research
NIH ECHOs: Lifecourse epidemiology of adiposity & diabetes center (Dabelea); Developing brain (Deoni)	Population approaches to preventing obesity and diabetes; Development of the brain as assessed by imaging, liked to databases
College of Nursing	
Healthy mother-infant interactions: **(**Gance-Cleveland, Gauthier, Aldrich, Neu, Trego)	Prenatal screening and early intervention; Reduction of childhood obesity/CVD risk through school health programs; Nutrition/physical activity in special-needs children

D. APPROACH.

Governance: Dr. William Hay (see **Biosketch**) will direct the ELEP, reporting to the CCTSI Exec. Committee and Dr. Sokol, PI. Dr. Hay has directed the Perinatal CTRC program since shortly after its inception in 1970, and developed and directed the CCTSI CMH Program during its first two cycles. He also chairs the *ELEP Planning and Oversight Committee*, with representation from across the CU-AMC and CCTSI from the Perinatal CTRC, Pediatrics, ObGyn, Medicine, Psychiatry, Pharmacy and Pharmaceutical Sciences, Dentistry, Nursing, School of Public Health, Native American affairs, and community partners. **Dr. Theresa Powell**, an internationally recognized basic and translational scientist, serves as the ELEP Co-Director, leading the Perinatal Research Facilitation Committee and the Perinatal Research Network Planning Program (see **Biosketch**). A complete organizational chart is in **Facilities & Other Resources**.

Director and Chair, Planning and Oversight Committee: William W. Hay, Jr. MD (Pediatrics, Neonatology, Perinatal Biology/Medicine; Perinatal T32, CHRCD K12)

Co-Director and Chair, Perinatal Research Facilitation Committee and Perinatal Research Network: Theresa Powell PhD

Pregnancy (maternal, fetal, Labor & Delivery, placental) research: Theresa Powell PhD (placental biology; origins of obesity); **Lorna Moore PhD** (high altitude/hypoxia effects on pregnancy and uterine function)

Linda Barbour MD (Maternal Obesity/Diabetes, Fetal Overgrowth)

Neonatology research: John Kinsella MD (nitric oxide, Cong. Diaphr. Hernia)

Pediatric research: Peter Mourani MD (CHCO Res. Inst. Med. Dir.; lung disease)

Aim 1: Expand and streamline our broad-based, multidisciplinary organizational structure to promote Early Life Exposure Clinical-Translational Research in the CCTSI.

1.1. Develop the Perinatal Research Network (PRN) to promote research in ELE research across the campus and the CCTSI institutions and collaboratively with national CTSA programs. The purpose of the PRN is to create an interactive network of investigators at CU-AMC interested in pregnancy and early life exposures and origins of disease to support: a) collaborative efforts that span Departmental, School, and Institutional barriers; b) research infrastructure that includes a Data/Biosample repository to collect/store/share samples and data collected for targeted studies that are of interest to multiple investigators, and are essential for CTSA collaborations; and c) platform for exchange of knowledge gained about diseases with onset at the beginning of life (conception to 2 years of age) with their later life health consequences. The PRN will facilitate collaboration, ensure fair and responsible recruitment procedures, and provide a safe and supportive environment for pregnant women and their young children to participate in clinical-translational research. These unique participants require specially trained and dedicated investigators and research staff to support their participation in research. A new tool for centralized surveillance and recruitment has been developed (see PARITY below) that ensures equitable distribution of consented subjects and their biological samples to all studies. This contemporary EMR-derived database and bio-sample repository will facilitate collection of preliminary data to determine study feasibility, support individual grant proposals, and support current and future collaborative, interdisciplinary research among related research groups between CU-AMC and other CTSA Hubs. The PRN will provide a unified research infrastructure to support studies through a fee-for-service and collaborative network with access to 1) research coordinators/assistance with expertise in perinatal studies, 2) screening and recruitment staff, 3) outreach to community providers for study recruitment, 4) 24/7 perinatal research nurse support, 5) engagement of clinical teams in research, and 6) management and analysis of clinical data. The benefits of campus wide coordination, an oversight committee, and managerial study personnel are exemplified by the needs for 1) general consent and standardized protocols for use of EMR data and collection of non-invasive biosamples such as cord tissue, cord blood, and placenta, 2) collaborative mechanisms to share samples and results across multiple studies, and 3) coded sample aliquots with storage technology for "sharable" samples linked to coded PHI data, imaging, clinical lab data, and experimental results. Optimizing sample and data collection, storage, and use by collaborative groups requires expertise in database management, which will be supported by recruitment of a dedicated ELE data base manager. Access will be web-based with detailed inventory of projects that are active, pending, and completed, and will contain contact information for PI's, including a population overview, a data dictionary, limitations, and contacts to request access or information. Streamlined procedures and a collaborative forum to initiate and carry out research using this data/biosample repository will be the basis for exploratory pilot studies, obtaining preliminary data, and supporting the development of multi-disciplinary and individual grants.

1.2. Working Groups: Objective: To develop research programs and training opportunities focused on early life exposures and developmental programming. We plan to create functional working groups to synergize research efforts and reduce redundancy of research infrastructure. The following are existing groups

that will be incorporated into the PRN: Colorado Program for Nutrition and Healthy Development, Colorado Institute of Maternal Fetal Health/Fetal Care Center, Adolescent Medicine, University of Colorado Altitude Research Center, Children's Outcomes Research, Global Health Research, and the Kempe Center for Child Abuse and Neglect. A major new effort will be to engage the CU-D Center for Personalized Medicine and their Bio-computing capabilities for genetic and health-related datasets (Drs. Barnes, Kahn, Taylor) that will enable expansion of early life exposure research into precision medicine initiatives, pharmacogenomics, anthropologic genetics, and biomarker discovery.

1.3. Single Disease Working Groups: Objective: To identify single diseases with significant strengths in ELE research at CU-AMC and facilitate collaborations to enhance novel ELE research opportunities. Research across the CU-AMC involves the entire span of maternal/pediatric health and adult disease and applies methodologies ranging from basic science to translational/clinical science to health outcomes and public health research. ELEP will provide pilot funding through the CMH Pilot grant program to create interdisciplinary groups focused on a single disease that will work toward treatments in pregnancy and early life to improve fetal and neonatal development and lifelong health. They will strive to understand environmental impacts after birth, including the physical environment, diet, trauma, drugs, childhood psychosocial exposures, etc., that lead to multiple health risks throughout the lifespan. Interested groups will compete for this pilot funding, using CCTSI sponsored Team Science training and Studio projects to enhance their approaches to research focused on the life course of their specific diseases.

Aim 2: Provide coordinated research support and development.

Support for ELE research will include **expertise in data and biorepository management** to provide resources that PIs can use for funded, targeted studies. A **Shared Informatics Platform** will identify and track data and specimens across multiple funded studies (PARITY—see below—will use COMPASS to electronically retrieve data from mothers and infants, linked to each other and their samples). **Linked resources to common life course mechanisms** and a **website with life course research resource links** will support investigators with study design, initiation, funding sources, analysis, and publications. Specific resources will include:

1. **Child Maternal Health (CMH) Pilot Grant Program for early career investigators:** to provide pilot funding for promising ideas, primarily for junior investigators (**see Component D.** Translational Endeavors: Pilot Translational and Clinical Studies).
2. **Children's Clinical Research Organization (CCRO).** The CCRO at CHCO provides comprehensive research services, facilities and personnel to support the facilitation and conduct of clinical research, including study start-up, contracting, execution, and close-out for research conducted primarily at CHCO.
3. **Develop and maximize enrollment of pregnant women in the PerinAtal RegIsTrY Program (PARITY).** The primary objective of the **PARITY program** is to establish a cohort of consented pregnant research participants, including contact information and clinical data, comprised of women who initiate their prenatal care at the UCH outpatient pavilion and the CHCO Adolescent Maternity clinic, with the intent to compile pregnancy linked to childhood data for up to age 5 years. PARITY aims to improve the efficiency of conducting research by: providing a single, centralized recruitment database for clinical trials involving pregnant women and their young children; creating a prospective dataset for observational studies; and developing a mechanism for future maternal and/or neonatal studies using prospectively-collected data for longitudinal case-control studies of neonatal/childhood disease; and for tracking outcomes backwards to prenatal life. Once enrolled in PARITY, demographic information and specified outcomes will be collected through an automated process supported by the Health Data Compass, the data warehouse that integrates patient clinical data from both UCH and CHCO (**see Component B. Informatics**). Data will be automatically pulled monthly from the EMRs, uploaded into a REDCap database, then managed and disseminated by a skilled database manager. Any ELEP researcher may submit data-access requests to obtain de-identified data from PARITY.
4. **Provide Research Project Support through the Perinatal CTRC.** Details located in **Component F. Hub Research, Participant and Clinical Interactions.**
5. **Ensure fair, equitable, and ethical research subject allocation through the Perinatal Research Facilitation Committee (PRFC):** The PRFC assists investigators who are recruiting pregnant or postpartum women and their babies into research studies. Initial review is requested for all research studies on perinatal subjects across the CU-AMC to determine the feasibility of the proposed research protocol by: a) helping investigators develop realistic recruitment goals; b) validating that the study can be accomplished within the desired timeframe; and c) promoting collaboration among investigators with overlapping enrollment criteria. It establishes priorities for research protocols, assures that investigators are fully aware of existing data and biobank resources, and when necessary, directs investigators to alternative resources and/or research sites.

6. Promote sample use through the Child Maternal Health Sample Repository: The Perinatal Research Network will develop a pooled IRB-approved **Biosample Repository**. The CTMS OnCore will be used to catalog availability of samples and facilitate tracking of use, including those from funded studies stored within individual laboratories, thereby maximizing use of these valuable and limited specimens. Samples will be linked securely to the PARITY database. Maternal biological samples will include peripheral blood, urine, and buccal swabs. Delivery samples will include umbilical cord blood and segments, placenta, and myometrial tissue. Postnatal samples include maternal and infant blood and urine samples, infant tracheal aspirates, and maternal and infant body composition analyses. Mechanisms will be developed to enable ELEP investigators to apply equitably for access to shared samples and collaborative resources.

7. Maintain existing data/specimen availability through the Perinatal Database (PND) and Baby Blanket (BB): The **PND** consists of data collected by interview or EMRs for women (~22,500) delivering at UCH from 3/2005 – 12/2012. The **BB** cohort (with available blood specimens) includes 1128 women recruited at their first prenatal visit from 1/2011 to 5/2013 with planned delivery at UCH. Blood samples from one or more trimesters for these cohorts have been stored at -80^{o} C. These data and specimens have been used to generate 35 publications. The data and specimens remain available for future studies to advance understanding of clinical disorders and the health of pregnancy and infancy.

8. Expand collaborations with the Obstetrics Research Team to promote interdisciplinary research teams that will share research study nurses and research staff, collaborate with the PCTRC research staff, and use the research services orchestrated through the PRN.

9. Expand collaborations with the Colorado Institute for Maternal Fetal Health (CIMFH) and the Colorado Fetal Care Center (CFCC) in studies of neurodevelopmental outcomes, maternal/and paternal depression and anxiety, and quality of life measures of infants, parents, and families in NICUs and CFCC.

10. Establish mechanisms for collaborative studies among national CTSA networks through the CTSA Lifespan Domain Taskforce, the NIH disease-specific and rare disease networks, and other CTSA hubs with NIH ECHO grant recipients. To assist in these activities and promote new collaborations, we will expand the ELEP Website to include relevant child/maternal/lifespan research, education, and training opportunities, identify ELEP investigators at the CU-AMC and in the CCTSI, and promote the availability and awareness of ELE research in our combined programs. A prime opportunity will be to collaborate with the Cincinnati CTSA Lifespan Data Integration Module of maternal and offspring health information, environmental exposure data, and social determinants of health and disease, which is developing a population-based data resource defined by the linkage between vital statistics (birth records) and hospital delivery EMRs (from both mother and infant) (Dr. Lou Muglia, Director; see Letter of Collaboration). We also have an opportunity to collaborate with the Utah CTSC (Dr. Will Dere, Director), their extensive genetic, maternal-infant, and lifespan data from Intermountain Health Care (Dr. Michael Varner) with linkage of all University of Utah and IMHC electronic medical records (1995–present) to the Utah Population database, which includes a range of records that allow assessment of early life circumstances and later life health for historical and contemporary cohorts, and their leadership in the CTSA Lifespan DTF ELE Working Group and Lifespan Tool Kit Project (Dr. Heidi Hanson, Dr. Julie Shakib, Utah; W Hay, Colorado). A goal would be to combine our 3 institutions in an application for a U01 or CTSA Innovation and Collaboration Award to support future research in early life exposures and later life outcomes.

Aim 3: Foster new education and training opportunities in Early Life Exposures research. This aim will provide an educational platform to enhance the exchange of ideas, education, and collaborations with investigators invested in ELE research (locally and among CTSA institutions). Practical approaches will help optimize investigators' capacities to plan research with appropriate scientific justification, study design and research conduct (Regulatory-Compliance, ELEP Research Coordinator/Advocate), data analysis (CCTSI Biostatistics and Informatics education, and analysis through the Personalized Medicine Initiatives), and dissemination of data. A new **Campus-wide CMH Research Coordinator/Advocate** will support investigators (advice on study design and execution to assure high scientific quality and adequate protection of research participants, support collaborative efforts across the campus, reduce institutional barriers, and coordinate research projects that span clinical units and sub-specialties) and research subjects (contact person for all research subjects who have questions or concerns; design and implement programs to improve participant understanding of research; and ensure appropriate diversity among research subjects).

ELE research **education and training** opportunities will be incorporated in the CCTSI Translational Workforce Development Program (TWD) to assist investigators at all career stages. Objectives will include disseminating information about ELEP-related research being conducted throughout the CCTSI, providing opportunities for mentoring and assistance for junior faculty or fellows, linkage to the appropriate ELEP Working Group activities,

and coursework within the TWD educational portfolio. We will disseminate information about PRN resources, encourage collaborative interactions, promote establishment of funding streams, and invite external experts for symposia/workshops/seminars, including PRN and Working Group Symposia and quarterly interdisciplinary/ multidisciplinary educational conferences. The first symposium, planned jointly with the Building Better Babies program and the CCTSI, for May 2017, will include internationally recognized speakers, an interactive discussion panel comprised of community and hospital representatives, and early career presentations of basic mechanisms and clinical correlates underlying developmental programming of chronic diseases. The goal is to develop strategies that can promote novel, effective, and safe intervention strategies for pregnant women and infants to improve the health of mothers, their babies, and future generations. The PRN will provide mentoring to early career researchers to ensure development (and hiring) of critical faculty with new interdisciplinary translational skill sets. A new Perinatal Translational Science Course within our TWD program will be developed for early career and graduate students. Research Studios and team building resources (**see Overall Component**) will link pregnancy and early life studies with early life exposures and later life disorders to better inform hypothesis generation regarding health risks and, most importantly, novel preventative interventions.

E. ENVIRONMENT: Table 2: Summary of Existing & New Strengths & Future ELEP Plans.

Existing Strengths	**Comments**
CMH Pilot grants	CHCO RI support
Perinatal CTRC	CHCO RI support
Perinatal Research Facilitation Committee	Reorganized in 2015 with broader AMC participation
Individual Faculty Research Strengths	> 30 R, P, & U grants (> $18M)
Perinatal Research Programs/Training Grants	>10 T32/ K12 programs
CO Early Nutrition Program and Infant Gold Program	Friedman, Barbour, Hernandez
Healthy Start	Dabelea
NIH-NICHD K12 Women's Reproductive Health Research	Santoro
K12 Building Interdisciplinary Res. Careers in Women's Health	Santoro, Regensteiner
Baby Blanket and Perinatal Database	Santoro, Moore
Women's Health Research Center	Regensteiner, Reusch, Kohrt
New Strengths	**Comments**
NIH ECHO grants: LEADS Center; The developing brain	Dabelea; Deoni
ObGyn Department Expansion	Jansson, Su, Hurt
Neonatal Outcomes Research Alliance [NORA])	Powell, Hwang
Building Better Babies	Jansson
OB Research Team	Prenatal Clinic research staff; Santoro
MFM Clinical Research Director hire in 2017	TBN
PARITY Maternal Research Registry	Ob/MFM (Mansfield)
Future Plans	**Comments**
Shared Database and EMR electronic data retrieval (PARITY) COMPASS, Red CAP; Linked maternal EMR with child's EMR	Division of Biomedical Informatics and Personalized Medicine; hire database manager
Biorepository for pregnancy/early life samples linked to the PND.	Engage the BB and OnCore, and Personalized Medicine
Infrastructure for pregnancy and early life follow up studies	Perinatal Research Network
Support for PCTRC and OB research team - supervisory level	PRN coordinator/advocate
Platform for communication and exchanging ideas	BBB/PRN Symposium, May 2017
Education in Translational Perinatal Research "from animal models to novel therapeutics"	Early career training in translational DOHaD studies

F. TIMELINE AND METRICS/ EVALUATION: The ELEP will develop an interactive research support, training, and education network for ELE Research with an emphasis on prenatal and infancy developmental programming of adult disease. The **impact will be significant**, increasing the diversity of researchers who will have enhanced research capacity for pilot studies, individual research programs, and collaborative networks. Pregnant women and their children from all backgrounds, especially diverse and under-represented segments of the population, will have a secure and equitable system for participation in research. **Metrics for success** of ELEP will focus on the number of investigators using ELEP resources, evaluation of projects through the PRFC, new collaborations established through the linked data/biorepository, number of publications and new grants, and especially novel collaborative and interdisciplinary projects involving interventions and long term prospective trials to reduce the impact of ELE on adverse outcomes. Timeline for program initiation is:

Year 1	PARITY activation	Hire Coordinator and Database Specialist	Symposium 1
Year 2	Link PARITY to biosamples through OnCore program		Symposium 2
Year 3	Increase CU AMC groups using linked electronic data/ sample repository	UO1 grant developed	Symposium 3
Year 4	Establish disease-specific Working Groups across the lifespan	Develop DOHaD science training program	
Year 5	Maintain and expand PARITY and collaborations across the CTSA consortium		Symposium 4

COMPONENT H1: EARLY LIFE EXPOSURES PROGRAM

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COMPONENT H2: INNOVATION ECOSYSTEM (PIVOT)

PROJECT SUMMARY/ABSTRACT

The **Innovation Ecosystem (Partnering for Innovation Value Optimization and Accelerated Translation [PIVOT])** program will embrace innovation and commercial translation to advance biomedical discoveries into the marketplace. Through this Optional Function of the CCTSI, we will develop and sustain an innovation program to educate, train and develop our workforce in ***commercial value translation***; to support the technical development of commercializable innovation; and to demonstrate value and health impact of clinical and translational science innovation by providing access to accelerator venture capital funding, domain expertise, and commercialization mentorship. The overall goal of PIVOT is to provide a seamless, multi-level investigator-facing infrastructure supporting the commercialization and product development of innovative ideas and, in the process, support and academically reward entrepreneurship. We will achieve these goals through the following specific aims: **Aim 1**: Workforce. Catalyze an academic entrepreneur culture and workforce by (a) disseminating and expanding the reach of bio-entrepreneurship training opportunities, (b) fostering entrepreneurial networking, and (c) demonstrating career trajectories for faculty and graduate students who are clinical and translational science innovators. **Aim 2:** Development. Accelerate the development of commercializable innovation through customer discovery by Innovation-Corps (I-Corps™) teams and promote combined usage of I-Corps and Team Science training for innovation teams receiving CCTSI pilot awards. **Aim 3**: Demonstrate impact. Accelerate health impact demonstration through active navigation to resources within the CCTSI ecosystem which provide commercialization mentorship, domain expertise, and accelerator funding. The CCTSI PIVOT program will serve as an integrator-navigator and resource multiplier to expand and extend the reach of entrepreneurial investment and infrastructure support provided by University of Colorado and Colorado State University and the Colorado Office of Economic Development and International Trade. PIVOT will also capitalize on two unique NIH workforce training programs in Colorado: the Broadening Experiences in Scientific Training (BEST) award for graduate trainees in clinical and translational sciences; and the I-Corps™ Train-the-Trainer program at NCATS to develop a scalable short-course curriculum and common metrics adapted to the needs of clinical and translational science programs that will be disseminated across the CTSA consortium. In collaboration with an extensive network of state-wide, national and institutional innovation and entrepreneurship partnerships, PIVOT will lead a major academic shift within the CCTSI ecosystem by embracing innovation and commercial translation to advance biomedical discoveries into the marketplace. We will foster a culture that supports startup incubation and provides education and practical training to help academic ventures develop commercially-viable products and services.

COMPONENT H2: INNOVATION ECOSYSTEM (PIVOT)

SPECIFIC AIMS

We, and our collective institutional senior leadership, are leading a major academic shift within the CCTSI ecosystem by embracing innovation and commercial translation to advance biomedical discoveries into the marketplace, while maintaining an essential pipeline of basic, clinical and translational health research. Through this Optional Function of the CCTSI, we will develop and sustain an innovation program to educate, train and develop our workforce in ***commercial value translation***; to support the technical development of commercial-izable innovation; and to demonstrate value and health impact of clinical and translational science innovation by providing access to accelerator venture capital funding, domain expertise, and commercialization mentorship. The end goal is to provide a seamless, multi-level investigator-facing infrastructure supporting accelerated innovation translation **via commercialization and product development** and, in the process, support and academically reward entrepreneurship. We will achieve these goals through the following **Specific Aims:**

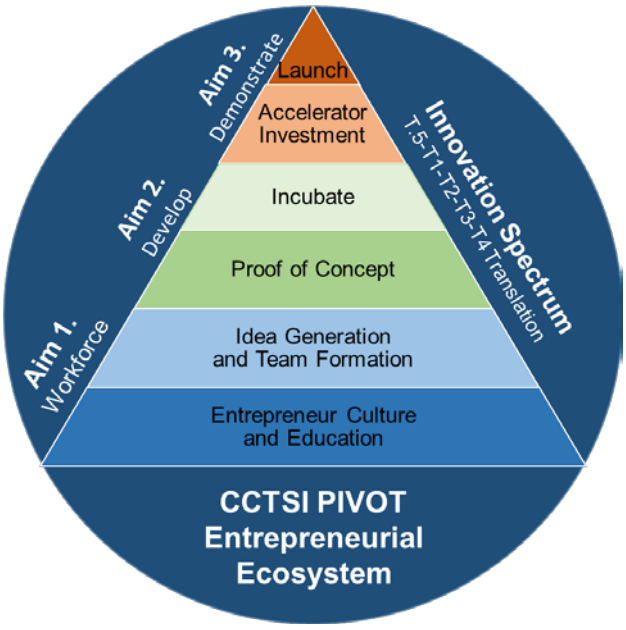
Specific Aim 1: Develop the Workforce. Catalyze an academic entrepreneur culture and workforce by (a) expanding and disseminating the reach of robust bio-entrepreneurship training opportunities, (b) fostering entrepreneurial networking, and (c) demonstrating career trajectories for faculty and graduate students who are clinical and translational science innovators.

Specific Aim 2. Develop Discoveries. Accelerate the development of commercializable innovations through customer discovery development support for Innovation-Corps (I-Corps™) teams and promote combined usage of I-Corps and Team Science training for innovation teams receiving CCTSI pilot awards.

Specific Aim 3: Demonstrate Clinical & Translational Impact. Accelerate health impact by connecting investigators to resources for commercialization mentorship, domain expertise, and accelerator funding.

PIVOT will serve as an integrator and resource multiplier in partnership with our collective institutional partners to expand and extend the reach of their commercialization investment. Figure 1 conceptualizes the CCTSI PIVOT entrepreneur ecosystem as a pyramid – where product launches build upon development and incubation which build upon an institutional culture that promotes individual, team, and organizational entrepreneurship.

Figure 1. CCTSI PIVOT Innovation Ecosystem



Best practice advocates for broad based strategies of innovator engagement that are aimed at enabling "entrepreneurial ecosystems" (1). The goal is to foster a culture that supports startup incubation and provides education and practical training to help academic ventures develop commercially-viable products and/or services (2). Mentors serve as business developers and provide more hands-on engagement than the typical business development coaches found in an 'investor-led accelerator'. In thriving academic ecosystems, interpersonal connections are key for success; faculty and graduate students learn about commercialization by observing the behavior of research leaders or by participating in entrepreneurial activities (3). The CCTSI PIVOT program will catalyze and foster these connections and peer role modeling.

Common Abbreviations used in this Component

BEST	Broadening Experiences in Scientific Training Program	CSU	Colorado State University	PIVOT	Partnering for Innovation, Value Optimization, and Accelerated Translation
CCTSI	Colorado Clinical and Translational Sciences Institute	CU AMC	University of Colorado Anschutz Medical Campus	I-Corps	Innovation Corps Training Program

COMPONENT H2: INNOVATION ECOSYSTEM (PIVOT)

RESEARCH STRATEGY

A. SIGNIFICANCE

Challenges exist in commercialization of academically-derived biomedical innovation. One key challenge is the failure to rapidly translate research innovation and discoveries into commercially-viable products and to move these through development, scale-up and dissemination into communities and clinical practice. CU and CSU, like many academic institutions, have created robust programs to support and facilitate translational research. However, the reality is that innovative ideas originating at academic medical centers are often met with seemingly insurmountable obstacles impeding their translation into improved patient care and health outcomes.

The trained physician or translational research scientist often has little knowledge about how to identify the commercial opportunities arising from their biomedical discoveries, including whether a discovery has potential for commercialization or how to advance solutions from concept to commercial venture. The frequent result is that the enthusiasm and expertise required to identify and potentially translate biomedical discoveries are lost in a complex process beset with significant barriers and substantial failure rates. Furthermore, researchers frequently jeopardize their academic careers when embarking on this translational path because current promotions and tenure policies do not formally reward (or may discourage) commercialization activities.

To overcome these barriers, the translational scientist of the future must be better trained to identify and develop commercial opportunities and be equipped to create viable public-private partnerships for more rapid translation of academic innovation into practice. Translational scientists must also be trained to advocate for entrepreneurism being part of their academic careers. To be sustainable, entrepreneurism and taking commercialization risks must be academically incentivized and rewarded.

The CCTSI ***Partnering for Innovation, Value Optimization, and Accelerated Translation (PIVOT)*** program signifies a Colorado academic institutional pivot in emphasis that is grounded in Colorado's historical excellence in clinical and translational research and discovery but moves us to a future where academic and commercialization endeavors are integrated for greater reach and health impact. Individual entrepreneurial-support providers within the CCTSI ecosystem have agreed to collaborate through PIVOT to form a new coordinated system of support for CCTSI investigators.

> *"... **the concept of the pivot**, [is] the idea that successful startups change directions but stay grounded in what they've learned. They keep one foot in the past and place one foot in a new possible future." --Eric Ries, StartUp Lessons Learned*

B. INNOVATION and C. PRELIMINARY DATA

The CCTSI is uniquely positioned to partner and catalyze an academic translational ecosystem for commercial value optimization and accelerated translation. PIVOT capitalizes on local economic investment and innovation priorities, a workforce motivated and poised for commercial translation, and NIH-funded commercialization training programs (e.g, I-Corps@NCATS and BEST). The following are existing and new resources that form the foundation for our evolving Innovation Ecosystem at CU-D and partners:

1. Colorado is a uniquely entrepreneurially-engaged state. Four Colorado cities are among the Top 10 with the highest densities of tech startups in the country (4). Denver has been recognized as one of the best places to launch a startup by *Forbes* (5). And Fort Collins is one of 6 featured "Places of Invention" recognized by the *Smithsonian* (6). Bioscience is a key Colorado industry: employing 27,000 people and representing $10 billion in payroll for the state. The CU Anschutz Medical Campus (CU-AMC) has filed >1,900 patent applications and formed 53 companies since 2002 and participated in 20+ SBIR/STTR projects with Colorado small businesses. The Colorado Governor's *Colorado Blueprint 2.0* prioritized the need to cultivate innovations and technology and foster Colorado's community of innovators, entrepreneurs and creative thinkers.

> "*There is a deeply rooted entrepreneurial spirit on this campus. Our history of innovation has led to important patents, powerful companies and discoveries that improve lives. But **the evolving health care landscape requires new models for innovation [translation],** ones that leverage our considerable assets*"- *Chancellor Donald Elliman, State of the Campus Address - 2016, CU AMC*

2. Colorado's Office of Economic Development and International Trade (OEDIT) has invested in several CCTSI-connected programs to strengthen bioscience commercialization infrastructure in Colorado:

- CU Innovations: StartUp Health Colorado. CU Innovations is the CU-AMC Technology Transfer Office. StartUp Health is a global organization focused on transforming healthcare delivery. It maintains the world's largest portfolio of digital health companies. StartUp Health chose Denver to be its second regional network affiliate and partnered with CU Innovations to bring together CU AMC, The Center for Innovation at CHCO and UCHealth CARE Innovation Center to create a heath innovation hub in Denver for digital health entrepreneurs, investors and industry stakeholders. The partnership focuses on developing healthcare startups and supporting CU-AMC innovators and staff with tools, resources, and programming.

> *"By providing an opportunity to help **develop and clinically validate impactful technologies** designed to solve the toughest problems in health care today, we can revolutionize the way care is delivered to our patients." -- Dr. Richard Zane, UCHealth Chief Innovation Officer*

- The Colorado Institute for Drug, Device, and Diagnostic Development (CID4) is a unique non-profit entity founded by the State of Colorado that supports CCTSI members. Its mission is to promote the growth of the bioscience industry in Colorado by accelerating commercialization of new drugs, medical devices and diagnostics based on discoveries made at Colorado's research institutions. CID4 has 5+ years of experience in accelerating promising bioscience technologies to the market by providing seed funding and hands-on venture advisory services. Since inception CID4 has reviewed nearly 160 early-stage companies (private and university spin-outs). CID4's first portfolio company, was acquired by Medtronic in 2015.
- The Colorado Center for Drug Discovery (C2D2) at CSU is a unique preclinical drug discovery organization capable of advancing commercialization through collaboration between academic scientists and the pharmaceutical industry. C2D2 provides access to chemical libraries for screening compounds and molecular modeling and computer-aided design, synthesis and/or medicinal chemistry support including optimization of screening hits, development of new analogs, and scale up of compounds to support in vivo studies.
- The CU Cancer Center (UCCC), a collaboration between CU-AMC, CU-Boulder, and CSU. UCCC received funding to create a collaborative infrastructure called the Colorado Cancer Translational Research Accelerator. Its goal is to significantly enhance Colorado's ability to effectively translate promising cancer therapies to the private sector. Funding supports biomarker identification and pre-clinical development of candidate compounds and immunotherapeutics from UCCC researchers; provides active project commercialization mentorship; assists start-up companies commercializing UCCC-originated compounds, attracting pharmaceutical company partners, and obtaining venture/angel funding.

3. The Gates Center for Regenerative Medicine (CU AMC) conducts stem-cell research to identify and manufacture novel therapeutic approaches for treating diseases and degenerative conditions. It was the first to test drugs that target cancer stem cells. The Gates Biomanufacturing (GMP) Facility serves academic, clinical and commercial investigators, both Colorado-based and nationwide, looking to translate discoveries into clinical-grade products suitable for investigational use in humans. Developing therapies using the facility include: corneal regeneration, immunotherapies for treating cancer, and esophageal repair following tumor removal.

4. CSU Ventures leads technology transfer and commercialization endeavors at CSU and offers state-of-the-art incubator facilities for early stage partners and core research areas including:

- Biopharmaceutical Manufacturing and Academic Resource Center (BioMARC). BioMARC was created to fill an industry need for high-containment biologics manufacturing. BioMARC has numerous strategic partnerships, including commercial manufacturing.
- The Institute for Biological and Translational Therapies explores orthopedic application of stem cell therapies for animals and adults. The Institute is an incubator that tests applications in veterinarian patients. As those innovations show promise, they are then taken forward into human clinical application.
- The Catalyst for Innovative Partnerships (CIP) encourages research teams to collaborate with new public-private partners to solve complicated problems. The Institute for Genome Architecture and Function is one CIP team who is studying the organization of genetic material in the cell and how this affects the development and progression of diseases.

5. Lastly, CU directs two NIH workforce training and education programs in entrepreneurship.

- Broadening Experiences in Scientific Training (BEST) for Careers Inside and Outside Academia. In academic ecosystems, graduate students play a pivotal role in university spinoffs and marketable technology development, similar to that of individual faculty entrepreneurs (7). The NIH Workforce report also reported that just 26% of PhDs in biomedical research move into tenured and tenure-track positions in academia (8). However, the training of biomedical science graduate students is often still exclusively designed for academic employment.

CU-AMC is one of only **10 universities selected by NIH nationwide** for the BEST award. Educational programs in BEST have become institutionalized so they are sustainable after the award ends.

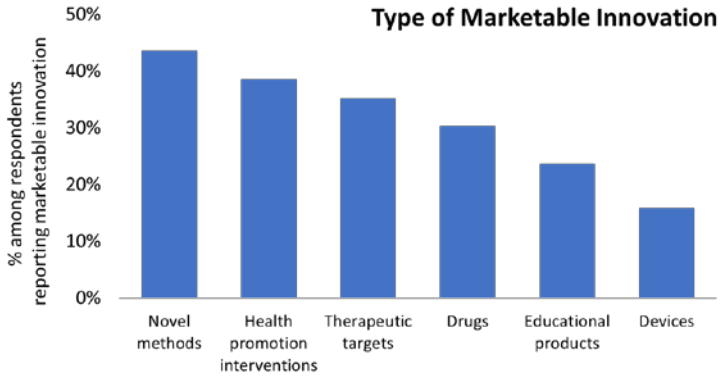
- Innovation-Corps (I-Corps™). The NIH/NCATS I-Corps program is a collaborative effort with the National Science Foundation (NSF) to support the commercialization of academic biomedical technologies. NSF launched I-Corps in 2011 to provide entrepreneurship training for NSF-funded scientists and engineers, pairing them with business mentors for an intensive 7-week, team-immersive curriculum focused on discovering a customer demand-driven path from their lab work to a marketable product. Over 500 teams have completed the curriculum, which is based on the "Lean Launchpad" model developed by serial entrepreneur Steve Blank at Stanford. This has resulted in the creation of over 260 companies that have collectively raised more than $40 million in funding from outside sources. NIH adapted the I-Corps program to focus on moving technologies developed through SBIR/STTR funding to the marketplace. The **CCTSI was one of 10 CTSA Hubs chosen for this NIH program**.

*The CCTSI is **among 10 CTSA's selected** nationally to participate in the **NCATS I-Corps Train-the-Trainer Program**. Aims of the administrative supplement are to adapt and tailor the curriculum and metrics to be appropriate for CTSAs; demonstrate feasibility, acceptability and scalability of a short-course starter program; and disseminate across the CTSA consortium.*

D. APPROACH

PIVOT capitalizes on the entrepreneurial spirit of the CCTSI ecosystem and members. The 2016 CCTSI Needs Assessment surveyed all CU-AMC researchers, CCTSI members, including CSU and affiliate institutions; 48% of respondents reported that "*the products or outcomes of my research and work are marketable*". Commercializability reflected the full spectrum of T0.5-T2-T3-T4 innovation as shown in **Figure 2**.

Figure 2. 2016 CCTSI Needs Assessment Survey Results



The CCTSI will serve as an integrator and resource multiplier in partnership with our collective institutional partners to expand and extend the reach of our commercialization investment. The CCTSI PIVOT entrepreneur and innovation ecosystem is conceptualized as an integrated pyramid – in which, product launches build upon development and incubation which build upon broad based culture and education -- see **Figure 1**, **Specific Aims.**

To be sustainably successful, academic entrepreneurial ecosystems must also pay attention to the character of research life offered by universities so that system-level infrastructure investments enhance, not detract, from the main sources of satisfaction and professional development that most scientists derive from their research endeavors (3). We charged a LITeS team to identify what is needed to catalyze an entrepreneur ecosystem from the faculty's perspective. [LITeS Teams are assigned case projects to address important clinical and translational research challenges within our institution – **see Components C. & I.**] Barriers to entrepreneurship that were identified included: "impenetrable bureaucracy (knowing where to go)", "lack of time and funding (knowing how to jumpstart development efforts)", and "academic disincentives (as they related to promotion and tenure)".

Using I-Corps business model methods, we developed the CCTSI's value proposition to address these "pains":

PIVOT Value Proposition. For *academic clinical and translational scientists* (our customers), **CCTSI PIVOT provides** *entrepreneur training/mentorship*, *product development support*, and *navigation to hands-on domain expertise and financial resources* (our products) necessary for successful commercialization in order to *accelerate the health impact of their innovation* and *contribute to a satisfying academic career* (benefits for our customers).

Aim 1: DEVELOP THE WORKFORCE. Catalyze an academic entrepreneur culture and workforce by (a) expanding and disseminating the reach of robust bioentrepreneurship training opportunities, (b) fostering entrepreneur networking, and (c) demonstrating career trajectories for faculty and graduate students who are clinical and translational science innovators.

1.1. Expanding training opportunities. PIVOT will support entrepreneurship as a clinical and translational sciences core competency by providing, in collaboration with the CCTSI Translational Workforce Development

Program **(see Component D. Translational Endeavors**), experiential training for innovators (including teams) and by disseminating other local bioentrepreneurship training opportunities. **Table 1** shows training opportunities by targeted learning segment.

Table 1. CCTSI Innovation Training		Level of Training-Education	
		Introductory	Advanced
Type of Learner	Individual	• BEST Bioentrepreneurship Workshop • CU Innovations seminars	• CU Innovation Fellowship • Bioentrepreneurship Graduate Certificate
	Team	• I-Corps@CCTSI • Team Science	• National I-Corps™ (NIH/NSF) • StartUp Health Colorado Academy

a. Training for Individuals

BEST Bioentrepreneurship Workshop. The BEST program created introductory-level training in the form of career seminars, workshops, and graduate courses. There is a multi-day workshop for trainees on *Life Science Development and Commercialization* taught by the President and Co-Founder of the national Society of Physician Entrepreneurs (SOPE) who is a CU-AMC emeritus professor. CU Innovation Seminars hosts monthly seminars with invited entrepreneur speakers. The CU Innovations Fellowship is a competitively-selected, 4-month paid fellow-ship designed for graduate students in health sciences, intellectual property law or engineering and MBA students with a technology or startup background. Fellows gain experience in marketing and commercializing top university biotechnologies, get involved with new ventures and startups, and connect with industry partners. The CU Bioenterpreneurship Graduate Certificate is a CU-Denver program for academic health professionals that is taught by faculty from the Jake Jabs Center for Entrepreneurship at CU-D in collaboration with faculty from CU-AMC. To complete the certificate, students take *Building Biotechnology* or *The Legal and Regulatory Environment of Life Science Innovation*, two entrepreneurship electives, and *Business Model Development and Plan* or *Corporate Entrepreneurship* as their capstone.

b. Training for Innovation Teams

*A CSU innovation team led by David Frisbie, DVM, PhD, Director of the **Institute for Biologic Translational Therapies**, won the **Top Team Award at NSF I-Corps among the 2016 Spring Cohort in San Francisco**. They received incubator funding from the Colorado Advanced Industries Accelerator to move their product forward.*

I-Corps is a team-based immersive learning program taught by faculty with an entrepreneurial background. The program prepares teams to compete for SBIR/STTR funding. I-Corps@CCTSI launched in 2016 at CU-AMC and we are expanding the program to CSU in 2017. Three training cohorts, (2 at CU-AMC and 1 at CSU with 8-12 teams each) will be held each year. To date we have trained 19 teams representing a spectrum of T1 to T4 innovation. I-Corps@CCTSI is a 3-week introductory short-course to help teams identify their target customer and through a customer discovery process involving 30 interviews test their "value proposition" hypothesis. With support from the CU-AMC Chancellor Elliman, we partnered with a national NSF-NIH I-Corps trainer from U California Berkeley who trained us so that our CCTSI I-Corps teams can qualify for the national 7-week NSF I-Corps program ($50,000 award) which helps teams create a complete, scalable business model.

Team Science. Today's investigators are generally trained in siloed-disciplinary approaches and have little formal training, or exposure, to teams processes and skills (9). Commercialization requires that innovators learn how to form teams, communicate, and work productively with product development and commercial partners. I-Corps and other entrepreneur teams will be encouraged to participate in the immersive Team Science training (see **Component C. Community & Collaboration**).

StartUp Health Academy. Digital health innovators at CU-AMC can apply for this competitively-selected advanced mentoring educational program. Teams receive business coaching on telling their value proposition story (:59 sec, 4 min, 8 min versions); quarterly business scorecard development and action plan assessment.

1.2. Fostering Entrepreneur Networking and Role Modeling

Active promotion of entrepreneur teams. Working in coordination with our PIVOT Council partners, the CCTSI will co-promote "testimonials", "lessons learned" and "success stories" in written newsletter and video story formats using resources from its administrative Communications and Dissemination Cores (see **Component A. Administrative Core**).

Annual PIVOT Innovation Summit. This approach re-applies the successful CCTSI CU-CSU Summit, a daylong conference aimed at promoting new collaborations across institutions. The CCTSI will hold a summit each year with its PIVOT Council partners to showcase and role model entrepreneur activities. We aim to foster new collaborations, both internally and externally, with entrepreneurs from the Colorado ecosystem.

Searchable entrepreneur PROFILES tag. The "Colorado PROFILES" search engine for biomedical research expertise at CU provides tools to help investigators and students find experts, potential collaborators or mentors, and to view past and present research networks of our investigators. It receives > 10,000 hits each month. We will leverage PROFILES and develop and promote the use of a common "entrepreneur" tag to facilitate easy searching, for entrepreneur partners and to evaluate growth in our entrepreneur ecosystem.

1.3. Demonstrating Academic Entrepreneur Career Trajectory

Graduate Student Internships. The BEST "*Internship - Technology & Innovation"* course provides graduate students the opportunity to intern in an industry as part of their doctoral studies.

Faculty entrepreneurship sabbaticals and entrepreneurial leaves of absence. PIVOT will develop and promote policies in support of entrepreneur sabbaticals and leaves of absence at CU and CSU. The U.S. Department of Commerce reports that progressive academic institutions: "allow faculty time off to engage in innovation and entrepreneurial activities, without incurring any penalty towards tenure and promotion. Providing leave to pursue entrepreneurial activities increases the potential for the successful technology development and commercialization of research, while adding to faculty's understanding of the commercialization process, enabling them to incorporate new material into student instruction. This flexibility also improves the focus of academic R&D efforts and facilitates public trust" (10).

Entrepreneurship Promotions and Tenure Track for Faculty**.** PIVOT will develop entrepreneur examples of excellence in education and research and criteria and metrics that can be used by promotion and tenure committees. PIVOT and Dr. Sokol, PI, will work with CU and CSU institutional leaders to advocate for the development of a new advancement track that rewards entrepreneurship accomplishments.

Aim 2. DEVELOP DISCOVERIES. Accelerate development of commercializable innovation through customer discovery support for I-Corps teams and promote combined usage of I-Corps and Team Science training for innovation teams receiving CCTSI pilot awards. This approach re-applies the successful Community Engagement model which requires training linked with their pilot grant programs and has resulted in the highest return on investment of any of the CCTSI pilot-supported grant programs.

2.1. I-Corps Customer Discovery Development. I-Corps@CCTSI teams will be eligible to apply for a new program of funding (up to $3000 each) to support their customer discovery process or concept validation. Following the national I-Corps model, teams may use the funds to support various activities, including attendance at a national conference to conduct customer interviews or to off-set time spent by a student, post-doc or research associate in development of the innovation's value proposition. Support can also be used for proof-of-concept validation necessary for advancing commercialization goals and seeking follow-on funding. I-Corps@CCTSI leadership will review these requests and provide funds as available.

2.2. Integrate commercialization training with the CCTSI pilot award program. CCTSI CO-Pilot, Novel Clinical & Translational Methods Pilot (NCTM-Pilot) and Community Engagement Pilot (CE-Pilot) program awardees (**see Component D**.) will be invited and encouraged to participate in the I-Corps and Team Science training to develop a business model for further development and commercialization of their research.

AIM 3: DEMONSTRATE CLINICAL & TRANSLATIONAL IMPACT. Accelerate health impact by connecting investigators to resources for commercialization mentorship, domain expertise, and accelerator funding.

3.1. Mentorship and Domain Expertise. Mentorship by experts is critical for early stage entrepreneurs. PIVOT leadership and *Innovation Facilitator* will assess each team's preparedness and refer them to outstanding resources recently developed in the Colorado Innovation Ecosystem. Examples of available resources include: CU Innovations has hired several Entrepreneurs-in-Residence available to CU CCTSI faculty and has developed a cadre of over 100 local entrepreneurs for customized domain expertise. StartUp Health Colorado innovators receive lifetime access to the StartUp Health Academy for mentorship and access to a global network of over 30,000 industry leaders, investors, customers and partners like AARP, GE, Janssen Research & Development, and others. C2D2 at CSU is comprised of former pharmaceutical industry scientists who consult with emerging drug discovery teams. CID4 staff dedicate 2,500 hours each year to advising both portfolio and non-portfolio early-stage bioscience companies and entrepreneurs. CID4 works closely with institutional technol-ogy transfer offices on patent strategies, company formation, business planning, regulatory issues and financing, and providing introductions to potential partners and investors, including federal and state small business grants.

> ***CU Innovations Entrepreneur-in-Resident****: Wayne Guerra, MD, MBA. An Emergency Physician and Co-founder and Chief Medical Officer of iTriage, a mobile app providing a symptom-to-provider pathway for users, acquired by Aetna in 2011.*

Accelerator Funding. The PIVOT *Innovation Facilitator* will assist CCTSI members in navigating and selecting funding sources, examples of which include: Colorado Advanced Industries Accelerator (AIA) Programs. The AIA program promotes growth and sustainability in bioscience to accelerate commercialization, encourage public-private partnerships and increase access to early stage capital. Grant funding is up to $180,000 ($135,000

state + $45,000 matching funds). Investigators are advised to work with their Tech Transfer Offices (e.g., CU-Innovations) for commercialization advice and support. StartUp Health Colorado. Innovators selected receive co-development, clinical validation and pilot opportunities for their companies from CHCO and/or UCHealth. Teams have access to the Digital Healthcare Transformer Pitch Day held every 2 weeks.

NIH SBIR/STTR Program. CID4 staff assist in Small Business Technology Transfer (STTR) and Small Business Innovation Research (SBIR) applications for seed funding from the federal government designated for small businesses and nonprofit research institutions who formally collaborate with one another. The Colorado Cancer Translational Research Accelerator and C2D2 provide Proof of Concept funding for PI-based research on novel targets for cancer and human disease. Seed grants are selected annually through a competitive, peer-reviewed proposal process. CSU Catalyst for Innovative Partnership teams are seeded with a critical mass of funding for two years and provided infrastructural support to seek partners and resources and create and deliver novel solutions in health.

Navigation example: *CU Innovations worked with CSU researchers to help partner them with clinicians at the Gates Center for Regenerative Medicine and Stem Cell Biology to receive accelerator funding to clinically scale-up a new approach to cancer immunotherapy.*

E. STRUCTURE AND GOVERNANCE

PIVOT will be directed by **Elaine Morrato, DrPH MPH,** who leads the I-Corps@CCTSI and CCTSI Dissemination Cores, in partnership with **Kimberly Muller, JD (Figure 3)**. Dr. Morrato (see Biosketch) is Interim Dean of the Colorado School of Public Health and has 15 years of experience developing and launching new medicines in Procter & Gamble's global healthcare division. She will report to Dr. Sokol, PI and the CCTSI Executive Committee. Ms. Muller, the Director of Technology Transfer at CU-AMC (the CU Innovations office), has more than 15 years of experience in intellectual property management, licensing, research partnerships with corporations, and the formation of venture capital-financed startup companies. She was formerly the Deputy Director of the Yale Entrepreneurial Institute, and Associate Director of New Ventures at Yale University in the Office of Cooperative Research, which has started >70 new ventures that have raised $5billion in investor capital. **Russell Korte, PhD,** an NSF I-Corps instructor and Associate Professor in Organization Learning, Performance, and Change program in the School of Education at CSU, will lead the I-Corps@CCTSI program on the CSU campus. **Kathryn Nearing, PhD** (CCTSI Evaluation and Tracking Core) will direct the evaluation efforts and is one of two evaluators invited to develop national I-Corps@NCATS metrics. PIVOT will also include staff to coordinate advanced entrepreneurial and experiential training activities, including the *Innovation Navigation Facilitator* (**Daniel Holtrop, MA**).

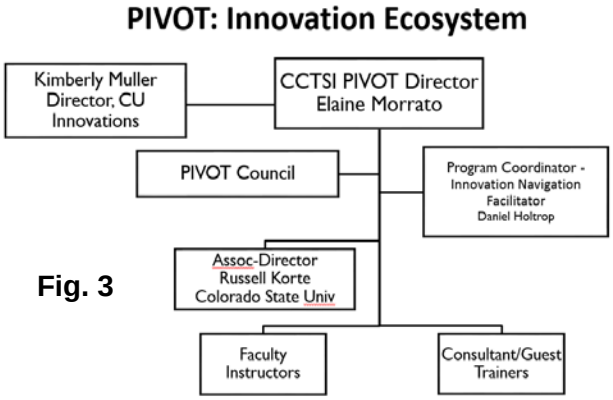


Fig. 3

PIVOT Council. Twice annually, we will convene a strategic leadership meeting with our innovation ecosystem partners: CU-Innovations, StartUp Health Colorado (UCHealth/Colorado Children's Hospital), CID4, the Colorado Cancer Center, BEST, Jake Jabs Bioentrepreneurship Program, CSU Ventures, C2B2, BioMARC, and the Institute for Biologic Translational Therapies. The purpose is to identify coordination opportunities for "wrap-around" support and for cross-promotion and dissemination of resources to ensure seamless integration.

F. TIMELINE AND METRICS / EVALUATION

Aims 1, 2 and 3 will be initiated in Year 1 and continued through year 5. The PIVOT evaluation plan builds upon the I-Corps@CCTSI evaluation. The PIVOT evaluation will examine the synergistic outcomes of incorporating I-Corps training within the PIVOT ecosystem. Linkage of the I-Corps@CCTSI and Team Science training with the CCTSI pilot programs represents a natural experiment. We will study characteristics of teams who opt-in vs. opt-out of training. To advance the science of commercial translation, outcome metrics will be compared. Nationally, a set of Common Metrics to evaluate the effectiveness and impact of the I-Corps@NCATS Program will be developed and we will adopt them. CTSA evaluators from CU-D and UC Davis will take the lead in developing metrics and evaluation tools: Specifically, Dr. Nearing will work closely with Dr. Julie Rainwater, UC Davis, who has nationally-recognized expertise in social network analysis. Short-term metrics for the I-Corps@NCATS program are to track the number of participants in the program, the number and diversity of teams trained, SBIR submissions, Invention Disclosures, and National and International patents. Longer-term outcomes include companies and jobs created, commercially-viable innovations, and private and public funding investment. The CCTSI will collect and report these Common Metrics and others to be developed.

COMPONENT H2: INNOVATION ECOSYSTEM (PIVOT)

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COMPONENT I: INSTITUTIONAL CAREER DEVELOPMENT CORE (KL2 PROGRAM)

PROJECT SUMMARY/ABSTRACT

Recent publications emphasize a shortfall in the number of investigators and scientists entering the clinical and translational research (CTR) pipeline. In response to the crisis, NCATS KL2 career development programs play an increasingly important role in preparing the next generation of clinical-translational scientists to be capable and resilient in the face of changes in health care, research funding and academic medicine. Our overall goal is to build upon the success of our CCTSI KL2 program and to provide in the next grant cycle a comprehensive **Institutional Career Development Core KL2** training program, for 5 KL2 junior investigator scholar slots for 3 years each at 75% effort, that will foster *outstanding* and *efficient* clinical-translational research education, promote clinical-translational science *competence* and *excellence*, and augment the *impact* of research performed by KL2 scholars. To achieve our goals, we propose 3 Specific Aims that are congruent with our conceptual model of CTR persistence developed by our CCTSI colleagues: **Aim 1:** Optimize the provision of individualized competency-based training in translational research methodologies, clinical trials, and data informatics, along with ethical, regulatory and Good Clinical Practice principles. **Aim 2:** Prepare KL2 scholars to thrive in the new collaborative research environment by fostering skill development in entrepreneurship, team-based science and mentorship. **Aim 3:** Assure that KL2 scholars develop and submit competitive grant applications to transition to independent investigators. These specific aims will be achieved through the use of individualized career development plans to facilitate KL2 scholar oversight and guidance by KL2 program leadership in completing milestones and goals. KL2 scholars along with their mentors, as a dyad, will complete the yearlong CO-Mentor program to solidify effective mentoring relationships. Immersion into CTR will involve meaningful CTR research experiences with the scholar's mentors to support the transition to independence. Innovative experiences, in the form of externships with community organizations and businesses/industry will be provided. Career development initiatives will be offered in team science, entrepreneurship, data informatics and translation through dissemination and implementation. All scholars will complete training in the responsible conduct of research and Good Clinical Practice. KL2 program leadership will be engaged in several activities to increase diversity including partnering with the School of Medicine's Office of Diversity and Inclusion and the University's Office of Inclusion and Outreach. All KL2 scholars will participate in the KL2 Curriculum, and many of the programs will be available to other junior faculty with NIH K or equivalent awards, enhancing CTR research training and collaboration across the CCTSI and the University. Key outcomes for the KL2 program will be the success rate of KL2 scholars in remaining in CTR positions, securing grants (transition to R and U type awards), number of peer-reviewed publications in high impact journals, development of intellectual property and racial and ethnic diversity.

COMPONENT I: INSTITUTIONAL CAREER DEVELOPMENT CORE (KL2 PROGRAM)

PROGRAM PLAN

SPECIFIC AIMS

Recent publications describe "a crisis" in developing and sustaining careers in biomedical research and the retention of clinician scientists. The crisis in part stems from a shortfall in the number of individuals entering the pipeline, despite creation of K08 and K23 programs in the 1990s to address this issue[1]. It is estimated that 1,000 individuals/year would need to enter the clinical scientist pipeline to maintain steady-state[2]. In response to the crisis, NCATS KL2 career development programs play an increasingly important role in preparing the next generation of clinical-translational scientists to be capable and resilient in the face of changes in health care, research funding and academic medicine. Training the translational workforce is challenging due to the multiple and diverse competencies needed for the T0.5-T4 research spectrum, the varying phenotypes of researchers, the widely varied backgrounds that trainees/learners bring to training, as well as the lack of clear career paths for some in these fields. We have a strong track record at the Colorado Clinical and Translational Sciences Institute (CCTSI) since 2008 in producing outstanding, successful clinical and translational scientists through the development of a robust and highly sought after KL2 career development training program.

In the next grant funding cycle, our overall goal is to further develop a comprehensive KL2 training program that will foster *outstanding* and *efficient* clinical-translational research (CTR) training, promote clinical-translational science *competence* and *excellence*, and augment the *impact* of research performed by the KL2 scholars. To achieve these goals, we propose the following **Program Specific Aims:**

Specific Aim 1: Optimize the provision of individualized competency-based training in translational research methodologies, clinical trials, and data informatics, along with ethical, regulatory and Good Clinical Practice principles.

Specific Aim 2: Prepare our KL2 scholars to thrive in the new collaborative research environment by fostering skill development in entrepreneurship, team-based science and mentorship.

Specific Aim 3: Assure that KL2 scholars develop and submit competitive grant applications to transition to independent investigators.

These specific aims will be achieved through the use of individualized career development plans to facilitate KL2 scholars in completing milestones and goals through oversight and guidance by KL2 program leadership. KL2 scholars along with their mentors, as a dyad, will complete the yearlong CO-Mentor program to solidify effective mentoring relationships. Immersion into CTR will involve meaningful research experiences with the scholar's mentors to support the transition to independence. Innovative experiences, in the form of externships with community organizations and businesses/industry, will be provided. Career development initiatives will be offered in team science, entrepreneurship, data informatics and translation through dissemination and implementation. All scholars will complete training in the Responsible Conduct of Research and Good Clinical Practice. KL2 program leadership will prioritize increasing scholar diversity including partnering with the School of Medicine's Office of Diversity and Inclusion and the University of Colorado Office of Inclusion and Outreach. All KL2 Scholars will participate in the KL2 Curriculum, and many of the programs will be available to other junior faculty with NIH K or equivalent awards, enhancing overall CTR research training and synergies across the CCTSI and the University. Key outcomes for the KL2 program will be the success rate of KL2 scholars in securing grants (transition to R and U type awards), retention in CTR positions, number of peer-reviewed publications in high impact journals, development of intellectual property and racial and ethnic diversity.

Common Abbreviations used in this Component

BEST	Broadening Experiences in Scientific Training	CO-Mentor	Colorado Mentoring Program
CTR	Clinical and Translational Research	ICDP	Individual Career Development Plan
CLSC	Clinical Science Graduate Program	PIVOT	Partnering for Innovation Value Optimization and Accelerated Translation
CFSP	Clinical Faculty Scholars Program	LITeS jr	Leadership in Innovative Team Science Program for Junior Investigators
CCTSI	Colorado Clinical and Translational Sciences Institute	SciTS	Science of Team Science

A. BACKGROUND

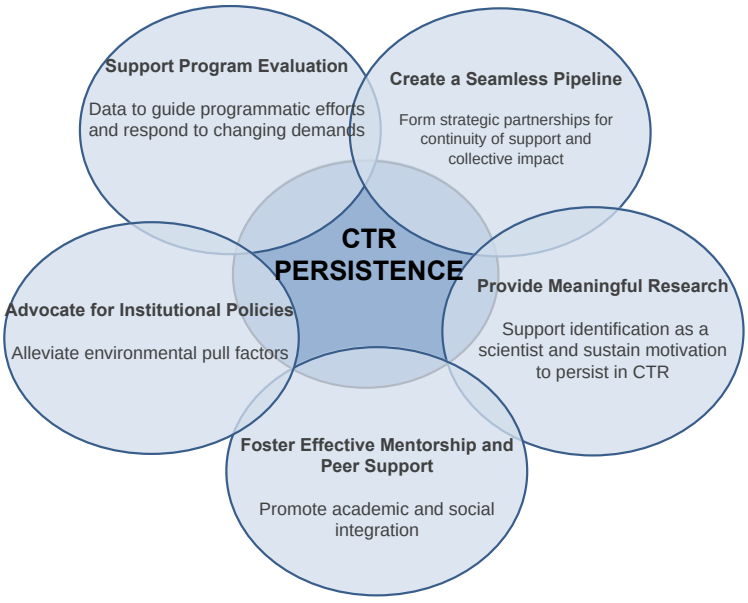
A.1. RATIONALE FOR A KL2 PROGRAM

To help build a sustainable clinical and translational research (CTR) workforce, we are requesting funding for five KL2 scholar slots and will use a conceptual model of academic persistence (Refer to Figure 1) as our theoretical framework developed by our colleagues, Drs. Nearing and Manson. This is an integrated model based on Tinto's theory of academic persistence[3-5]. The major tenet is that integration into the academic and social realms of the university strengthens commitment to the institution and the likelihood of academic or scholarly persistence. Participants in many clinical-translational science programs are initially attracted to a research career due to the thrill of discovery, naïve assumptions about autonomy and control over their professional lives, and a desire to make a difference[1] but then face challenges in transitioning to the next milestones and expectations. Our CCTSI colleagues, Nearing and Manson[6-7], have identified five overarching strategies that our KL2 program will apply in addressing this challenge of persistence in CTR and that will promote success of all scholars regardless of their specific research focus. These strategies were informed by our experience leading and evaluating programs across the educational and career development continuum, as well as by extensively reviewing the literature across multiple disciplines [3-5,6-13].

Vital Statistics for Previous CCTSI KL2 Scholars
100% remain engaged in clinical and translational research
590 peer-reviewed publications over 9 years
Scholars hold federal grants totaling $21.9 million

From this background work, the following five recommendations surfaced: (1) Create a seamless pipeline by forming strategic partnerships to achieve continuity of support for scholars/trainees and collective impact; (2) Provide meaningful research opportunities to support identity formation as a scientist and sustain motivation to pursue and persist in CTR careers; (3) Foster an environment for effective mentorship and peer support to promote academic and social integration; (4) Advocate for institutional policies to alleviate environmental pull factors (Environmental pull factors are the competing or conflicting demands with investigator engagement, integration, performance and, ultimately, persistence.); and (5) Support program evaluation—particularly, the examination of longitudinal outcomes—to guide such efforts and respond to changing demands[7]. Without a formalized plan to develop and sustain a research career, enthusiasm can wane over time. Though characteristics of the trainee are important, integration into the academic and social university fabric strengthens commitment and increases the likelihood of the KL2 scholar remaining in an academic environment. **Innovative aspects** of our educational programs will include the *interdisciplinary and team science* emphasis in our didactic and *experiential learning programs* coupled with the provision of a solid foundation in clinical and translational science didactic training. Our program will allow the flexibility to identify personal learning goals and individualize formalized learning experiences. All KL2 scholars will have mentoring teams that will integrate the scholar into the academic network.

Figure 1: Conceptual Model for Persistence in Clinical-Translational Research



Acknowledging published recommendations for best practices in training CTR investigators and learning gaps identified via needs assessments completed within our CCTSI community (scholars, mentors) conducted by the CCTSI Evaluation Core, we have identified **four areas of emphasis** for skills development: (1) Interdisciplinary team science; (2) Entrepreneurship; (3) Big data; and (4) Dissemination and implementation extending into community. These areas of emphasis will build on our existing infrastructure and align nicely with the overall CCTSI strategic plan and complement the educational competencies identified by the NIH and the work of the National Workforce Development Domain Task Force. The following articulates these **areas of emphasis** in more detail:

1. ***Interdisciplinary team science*** is essential for addressing many of today's complex biomedical and societal problems. By bringing together collaborators with diverse research backgrounds and perspectives, teams seek to blend their knowledge and creativity to push beyond the limits of current research. While team science promises individual and team benefits in creating and implementing innovations, its increased complexity poses challenges. Interdisciplinary and collaborative research creates additional challenges in conducting effective research that require even more sophisticated leadership and personal interaction skills[14-17]. Researchers increasingly recognize the need to master the skills needed for developing and implementing successful team science. For this reason, team science will be interwoven throughout our training program.

2. ***Entrepreneurship****:* It is increasingly apparent that translating discoveries into application is neither easy nor inevitable. To apply knowledge gained from research to impactful, practical applications, clinical-translational investigators must broaden their vision to embrace entrepreneurship. Entrepreneurship represents opportunities for learning and discovery that are usually novel to clinical-translational investigators but critical to the propagation of scientific knowledge into business and product development. Turning ideas into business ventures is tricky: only about 10% of budding entrepreneurs have a new firm in place within 12–18 months; the other 90% either fail to define a sound business model that can drive their idea forward to a new venture or realize their idea was flawed[18]. A key ingredient in successful entrepreneurship is self-knowledge. If clinical-translational investigators know their limitations and strengths, they may be able to avoid some common pitfalls in starting up a biotech company or business. Biological science is complex and rapidly changing and requires a specialized knowledge to understand the value of the innovation and its competitive position in the industry. Although life scientists are typically the founders of biotech companies, studies suggest that the most successful high tech startups are founded by a team of two to three individuals with mixed backgrounds, substantial industry experience, and a very clear market and product focus[19-20]. KL2 scholars will receive instruction about the pathways and processes, and lessons learned from entrepreneurship, for accelerating turning discoveries into applications that benefit society.

3. ***"Big data"*** is a term often used to describe the next transformative force in CTR and health care. The tapestry of potentially high-value information sources is exploding. Data contained in traditional health care systems including electronic health records, laboratory, pharmacy and imaging systems, and administrative/ billing systems will soon represent the *minority* of relevant individual-level data available electronically. Being added to these sources of information are continuously monitoring, wearable devices, such as Fitbit and Apple Watch; the burgeoning number of internet-enabled everyday devices as part of the Internet of Things (IoT) movement; and the explosive use of -omics technologies. Big data brings innovative opportunities for discovering new relationships across biological, clinical, personal, social and population-based data domains that were previously isolated in separate silos. Big data is not only BIG but also complicated with differences in structure, format, accuracy, completeness and even truthfulness. As such it requires new skills and knowledge across disciplines to realize its anticipated benefits for improvement of health.

4. ***Dissemination and implementation*** extending into community: Practice and policy concerns are growing over the "quality chasm," the gap between the promise of evidence-based medicine and the realities experienced in community practice. Community engagement increases the community's understanding of issues under investigation and enhances researchers' abilities to understand community priorities and conduct culturally appropriate and responsive research. Dissemination and implementation research has the potential to bridge the gap between clinical research, everyday practice, and public health by building a knowledge base about how health information, interventions, and new clinical practices, guidelines and policies are transmitted and translated for public health and health care service use in specific settings. Our program will provide education to develop skills in dissemination and implementation sciences and community engagement that can be applied across the entire T0.5-T4 translational spectrum.

Training the next generation of CTR teams, who will be able to support translation and implementation into clinical and community settings, requires a well-organized educational infrastructure, as described in further detail below. We will cultivate collaborations to improve the synergy of our educational programs and to continue to attract the most promising junior faculty to careers in clinical and translational science. Furthermore, we will enhance programs that promote and maintain excellence in regulatory knowledge and compliance. With the support of our Evaluation Core, we will continuously assess our successes and challenges to establish a flexible, responsive infrastructure. As a result, our career development program will nimbly adapt to the rapidly changing needs of future CTR. Given our experience and leadership in training and career development along the CTR pipeline[3, 6-7, 12-13, 21-26], we will continue to contribute to the evidence base by identifying and informing best practices in CTR workforce preparedness. We will build on our successes and educational infrastructure by

developing new and novel learning opportunities, identifying and demonstrating best practices for training, and disseminating our innovative programs to support identified needs of other CTSA hubs and academic settings. Through these innovations, we will make substantial contributions to strengthen the CTR workforce across CTSA hubs and at national and international levels.

A.2. BACKGROUND HISTORY: RESOURCES AND INFRASTRUCTURE TO SUPPORT KL2 PROGRAM

A.2.1. Preliminary Data. The CCTSI has built a comprehensive KL2 program for attracting, training and retaining highly competent KL2 scholars who persist in the field of clinical-translational research. ***All (100%) of our CCTSI KL2 scholars remain engaged in clinical and translational research***.

***Applicant pool*:** Preliminary data demonstrate that we have a highly qualified and diverse interdisciplinary pool from which to select our KL2 scholars (Table 1). The applicant success rate for our KL2 program is 16-19%.

Table 1: Characteristics of KL2 Applications According to Funding Cycle

Cycle	# applications	# women	% URM	% Disadvantaged	Departments
2007-08	31	19	3 (1)	3 (1)	10 peds, 13 med, 1 biostats, 1 epi, 1 surg, 1 path, 1 psych, 1 toxicol
2010-11	37	18	14 (5)	6 (3)	10 peds, 16 med, 1 ob, 2 surg, 2 anesthesia, 2 immunol, 1 pharm, 1 neuro, 1 env/health
2013-14	35	21	7 (2)	7 (2)	11 peds, 13 med, 4 surg, 2 neuro, 1 ED med, 1 immunol, 1 DVM, 1 genetics, 1 pub hlth
2016-17	32	18	4 (1)	14 (4)	11 peds, 12 med, 2 pharm, 4 surg, 1 bioinform, 1 genetics, 1 nutrition

CCTSI KL2 scholars have an enhanced and accelerated rate of success for the K to R grant transition, conduct research that is impactful to their fields, and are emerging academic leaders. To determine the national CTSA KL2 program success, faculty leaders from 48 CTSAs completed a survey regarding 914 KL2 scholars. For scholars who had completed their KL2 training two or more years ago, a total of 20.8% had received a NIH R01 or were a principal investigator on a project with a NIH program project or center grant. *For our first two KL2 CCTSI cohorts, a total of 57% (8/14) had received a NIH R01 grant or equivalent (U01), a success rate of almost 3 times the national average (Table 2).* Another indicator of KL2 training program success is the K to R transition time, i.e., the number of years for a K awardee to receive an R01 or equivalent award[1,27-28]. Prior assessment of training programs suggests that K to R peaks at about 8 years[1]. Our KL2 scholars transition from their K award to a R01 or equivalent more than twice as fast (average of 3 years) when compared to the national average. **We are among the top performing KL2 training programs as evidenced by 67% of our KL2 alumni scholars receiving NIH research funding within 2 years of KL2 completion**, compared to Sweeney et al.'s[28] report that 39% of KL2 scholars received funding within 2 years of program completion.

The success of the CCTSI KL2 program can also be evaluated by the return on investment for follow-on grant support. For our KL2 program, scholars achieve significant return on investment from federal funds that is sustained over time (Figure 2). As of October 2016, our 21 KL2 scholars hold $21.9 million of federal funding. Independent investigator awards, such as R01s, represent the most common type of award (Table 2). In addition to federal funding opportunities, our KL2 scholars have also successfully competed for prestigious local and national foundations including the Colorado Boettcher Foundation, Colorado Office of Economic Development, American Heart Association, Cystic Fibrosis Foundation, and the Michael J. Fox Foundation. Overall, our 21 KL2 scholars have received a total of 63 unique awards (an average of 3 awards per scholar).

Our KL2 scholars are making impactful contributions to the advancement of science through publication of clinical-translational research findings in diverse areas. (See Table 3) Advancement to leadership positions was explored as an indicator of KL2 career development for our scholars from 2008-2013 with 56% of scholars attaining new leadership roles since participating in the program. Examples of leadership positions held by KL2 alumni include: (a) from the 2008 cohort, Founding Director of Rehabilitation Science PhD Program at CU-AMC, Director of Colorado Biostatistics Consortium and Co-Director of Pediatric Stroke Program at CU-AMC; and (b) from the 2010 cohort, Director of Movement Disorders Center at CU-AMC.

Table 2: KL2 Scholar Federal and Non-Federal Grants Awarded, 2008-2017						
KL2 Cohort	**Years**	**KL2 Scholars**	**RO1 or Equivalent (U01) Awards**	**Other R Awards**	**Career Development (K) Awards**	**Non-NIH Awarded Grants by October 2016**
1	**2008-2011**	**N= 7**	**57% (4/7)** **3 R01** **1 U01**	**29% (2/7)** **2 R21**	**57% (4/7)** **3 K23** **1 K25**	**Total = 32 unique awards** Associations/Foundations: n=22 Universities: n=9. Industry: n=1.
2	**2011-2014**	**N= 7**	**57% (4/7)** **4 R01**	**29% (2/7)** **2 R21**	**29% (2/7)** **1 K02** **1 K23**	**Total = 18 unique awards** Associations/Foundations: n=11 Universities: n=4 Industry: n=3
3	**2014-2017**	**N= 7**	**14% (1/7)** **1 R01**	**29% (2/7)** **1R03** **1R21**	**0% (0/7)**	**Total = 13 unique awards** Associations/Foundations: n=11 Universities: n=1 Other: Department of Defense x1

*Table Source: NIH Reporter, accessed April 1, 2017. Table modeled after Schneider et al.[26]

Table 3: KL2 Publications Through January 2017				
Year	**# of pubs**	**# first author**	**# Sr. author**	**Ave. H-index**
2008	200	49	47	19
2009	113	24	32	16
2010	112	18	30	14
2011	67	23	11	11
2013	61	24	14	**
2014	37	11	6	**
Total	590	149	140	N/A
**** Too early to calculate**				

KL2 Vignettes – representing the value of the program:

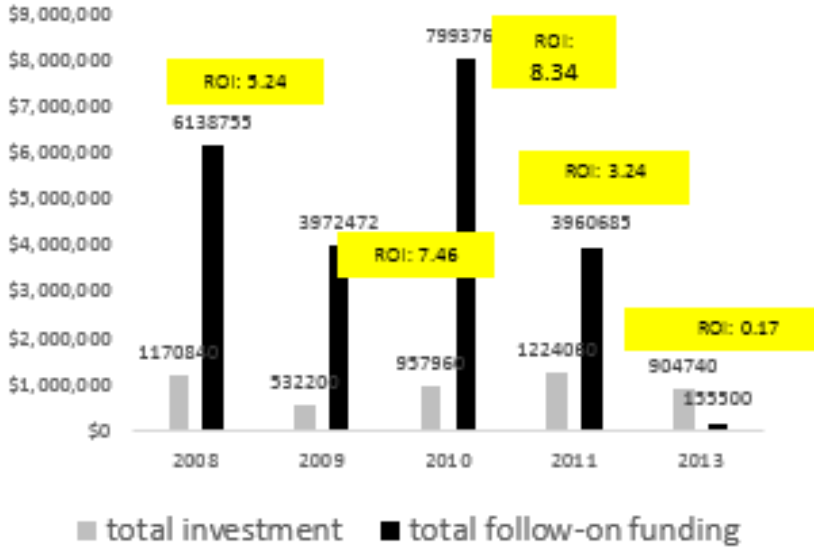
Magdalena Gorska, MD, PhD (Cohort of 2011): "KL2 was fundamental for my transition from a mentored to an independent research career. Thanks to the KL2 program I was able to establish my own research niche and generate necessary data for my first R01. It provided much needed financial support for my project as well as outstanding training for how to establish a successful career in academia. My success would not be possible without the KL2 program. For these reasons, I am very grateful to the CCTSI. The KL2 program is essential for the future success of junior faculty at the University of Colorado and National Jewish Health."

David Nichols, MD (Cohort of 2010): "My KL2 award provided critical support and mentoring in my early career to investigate an unexpected adverse drug interaction in people with Cystic Fibrosis (CF) that may impact over half of the entire US patient population. My KL2 work directly led to an ongoing multi-center clinical trial jointly supported by NHLBI and the CF Foundation. Our work is regularly highlighted in Year in Review sessions and articles from the American Thoracic Society and International CF conferences, underscoring the potential impact to our clinical and research communities. We have been awarded additional funding to study the mechanisms behind this drug interaction, which may have implications beyond those with cystic fibrosis."

Nichole Carlson, PhD (Cohort of 2008): "My KL2 provided me with two impactful outcomes. (1) Our research has changed how investigators now analyze neuroendocrine hormones as reproductive hormones. With our new approaches we can now quantify the hormone release mechanism for key hormones such as follicle stimulating hormones. This work resulted in a co-PI R01 to identify potential mechanisms of hormone disruption in obese women that lead to adverse offspring outcomes. (2) The statistical methods I learned during the KL2 translate well to analyzing lung CT images. We developed a new way of quantifying disease tissue in emphysema and sarcoidosis and are in the process of showing how these new methods are related to genetic and clinical phenotypes, which are likely useful clinical markers of disease progression. Outcomes of this work include; (1) formation of new collaborations (internally and externally); (2) personal attainment of independent research; and (3) development of new methods and analysis as the result of the KL2 work."

A.2.2. Supporting Institutions. The CCTSI has developed a large biomedical and clinical research infrastructure with the ability to address research questions across the T0.5-T4 continuum. Our strong CTR training programs bridge the entire spectrum of professional health and life sciences. The CCTSI partnership consists of CU-Denver (CU-D), CU Boulder (CU-B), Colorado State University (CSU), six hospitals and over 20 community organizations. **CU-D** is a comprehen-sive university within the region's largest metropolitan area, including the Downtown Denver Campus and the Anschutz Medical Center Campus (AMC). With more than 27,000 students and 100 degree programs in 12 schools and colleges, CU-D awards more than 3,400 degrees each year and more graduate degrees than any other institution in Colorado.

Figure 2: KL2 Program Return on Investment – Grant Funding



The **Downtown Denver Campus** is the most ethnically diverse college campus in Colorado, providing opportunities for improving minority and underserved population participation in training. **AMC,** a 230-acre campus with over $4 billion in capital and building investments, is the only Academic Health Education Center within Colorado. This is the central location of the CCTSI and is home to the CU health profession schools including the School of Medicine (**SOM**). Over 60 interdisciplinary research centers, institutes and biotechnology core facilities form the nexus for outstanding basic, translational, clinical and health outcomes research and training, which are integrated with many of the programs and core services of the CCTSI. An adjacent biotechnology park helps facilitate close collaboration between University investigators and the private sector. **CU-D Graduate School** offers 21 PhD graduate programs and five Masters programs. PhD degrees may be obtained in multiple basic and clinical science fields (including the Clinical Science PhD and Masters program). The **CU SOM/Office of Diversity and Inclusion** is striving to build an inclusive culture and not just implement a diversity strategy in danger of becoming a taskforce to count people. Thus, their activities are focused on the learning environment, curriculum, community service activities, and the institutional climate. Example activities include the **URM Pipeline of Programs,** which includes 15 summer undergraduate research programs, a rural health scholars program, and the Colorado Collegiate Health Professions Development. The **Colorado School of Public Health (CSPH)** was created in August 2007 as a partnership between CU-D, CSU and University of Northern Colorado. The CSPH plays a major role in training and career development in T3 and T4 translational research programs within the CCTSI, and houses the CCTSI Biostatistics (BERD) Program. CU-D also has additional interdisciplinary and interdepartmental programs, centers and infrastructure that will support the KL2 scholars. With substantial support from the recent Dean's research initiative, **Data Science to Patient Value (D2V)** was created with a core mission to position the university as a national and global leader in the development, implementation and dissemination of person-centered, high value health care by advancing innovations in data and health systems science to improve the lives of patient, families, and communities, and includes 6 cores to accelerate rigorous cutting edge data science methods and applications, which are available to KL2 scholars. In partnership with the UCHealth system, core areas of activity include: Patient and systems value; Stakeholder engagement; Analytics; Dissemination & Academic-Industry Collaboration; and Education. Another important program, **ACCORDS**, Adult and Child Consortium for Health Outcomes Research and Delivery Science, focuses on health services, comparative effectiveness, and dissemination/implementation research. ACCORDS', an interdisciplinary consortium of investigators, mission is to improve health, both locally and nationally, by supporting state-of-the-art outcomes and community translational research to guide clinical practice and policy. ACCORDS has 5 cores available to KL2 scholars: Research; Implementation and Dissemination Science; Education; Research Training; Practice Transformation and Community Engagement.

CU-B is a premier academic and research public University, including 8 schools and colleges and 44 doctoral degree programs. With 5 Nobel Laureates on the faculty, there is a rich history of innovative discovery leading to human applications in fields of biotechnology, medical research, biochemistry, biology, and bioengineering.

Interdisciplinary collaboration flourishes between CU-B and CU-D investigators and has led to major discoveries in bioengineering, tissue engineering, congestive heart failure, congenital heart disease, the microbiome, pharmaceutical biotechnology, and molecular biology.

CSU, which officially joined the CCTSI as a partner in 2013, is a public land grant institution founded in 1870 located in Fort Collins, a midsize city one hour north of Denver. CSU includes 8 colleges, including the renowned College of Veterinary Medicine and Biomedical Sciences. CSU also has leading research programs in animal science, occupational therapy and occupational health, health and exercise science, atmospheric science, clean energy technologies, neuroscience, health physics, environmental science, and team science. A translational initiative of their team science research is CSU's program of Science of Team Science SciTS) to be incorporated in the CCTSI, which will be provided to our KL2 scholars.

A.2.3. CCTSI Resources for KL2 Program. CCTSI has developed an extensive infrastructure and programs that will be leveraged by the KL2 program to sustain a high-impact translational workforce essential for a successful and vibrant research enterprise. This includes the following specific programs:

Leadership for Innovative Team Science (LITeS) is a premier opportunity for leadership training that permits assessment, development and refinement of leadership, management, and team-science skills and practices. The first CTSA program of its kind, LITeS was created to fill a gap and provide a leadership training program tailored for senior scientists. LITeS provides didactic and experiential work through 8 full day sessions over the course of one year to advance skills in 3 domains of competence: understanding of self, relationships with others, and executing work goals. During the new funding cycle, the CCTSI will work with other CTSA programs to disseminate this model. Because of expressed interest from others Hubs, LITeS was prominently featured in the CTSA Pipeline Series of manuscripts published primarily by Colorado authors in *Clinical Translational Sciences.*[26] LITeS is led by Judith Albino, PhD, president emerita of the University of Colorado, Professor in the Colorado School of Public Health, and PI for a NIDCR-funded center focused on oral health disparities of Native Americans. A psychologist, she is trained in executive coaching and has extensive experience in academic leadership, leadership training, and organizational consulting. Susan Johnson, PhD, Professor of Pediatric Medicine, and a LITeS alumna, is Associate Director of the program. Program evaluation shows that over half of participants apply their learning a great deal of the time, especially in managing interpersonal dynamics and within their own research teams. Over 70% reported enhanced social capital, an expanded network and increased connectedness because of the program. These factors are important, as they are predictors of persistence[6-7]. In the new grant cycle, to develop leadership and team skills for trainees, a LITeS-Jr program will be developed and provided to KL2 Scholars and other trainees.

CCTSI's Biostatistics, Epidemiology, and Research Design (BERD) core will provide KL2 Scholars with opportunities to collaborate and consult with biostatisticians to assist with study design and analysis and to participate in innovative training programs in biostatistics for non-statisticians.

Our CCTSI network of 5 **Clinical Translational Research Centers (CTRCs**) provides inpatient and outpatient research facilities and resources, which include dedicated inpatient and outpatient research space and equipment, research nursing, bionutrition, vascular ultrasonography and Core laboratories. **The CCTSI Translational Informatics Program** develops research informatics tools and provides training and support for research database and informatics needs. Resources that will be available to Scholars include: (1) **REDCap,** a web-based, HIPAA-compliant study data management solution adopted widely by members of the national CTSA consortium; and (2) **SeDLAC** (Secondary Database Library and Analysis Center) a system to access large national population-based datasets from NCVS and AHRQ. The team maintains approximately 20 servers running several applications for data management needs across the CCTSI, including backups, security, networking, access controls, and desktop support.

CCTSI Health Data Compass (Compass) is a multi-institutional data warehouse funded by the UCHealth System, Children's Hospital Colorado (CHCO), CU Medicine, and the CU-SOM, specifically designed to support data discovery and data sciences methodologies that integrate large-scale biological, clinical, administrative, regional, state and national data sets, such as environmental exposures and CDC data.

The **CCTSI's Regulatory Knowledge and Support Core (RKS)** helps KL2 Scholars navigate regulatory systems and requirements and provides training and consultation in the responsible conduct of research. Educational offerings (lunch hour workshops and short courses) occur every month throughout the year (See below Section D). Last year, over 700 people attended these offerings. A requirement of all involved in clinical-translational research at CU-D is the completion of the online CITI HIPAA, GCP and RCR modules in addition

to attendance at face-to-face workshops no less than every three years. Semi-annual conferences and Guest Lectureships are offered throughout the year to bring external scholars to the campus and to foster interest and development in the regulatory sciences. Our ethics conferences are oversubscribed with over 300 attendees.

Innovation Corps (I-Corps™). I-Corps@CCTSI is a team-based short course designed for faculty, staff and students, which guides teams through the early stages of customer discovery where they can test business model hypotheses for their technology or idea to accelerate the translation of innovations to clinical practice. I-Corps@CCTSI leverages and partners with the CU-D Innovations Office and the CHCO Center for Innovation. These partnerships facilitate collaboration, access to a large knowledge base and investor pool, access to proof-of-concept funds, and interdisciplinary expertise. Prior KL2 scholars have become very interested in the knowledge and experience imparted by our I-Corps@CCTSI program.

A.3. NEED FOR CCTSI KL2 PROGRAM

The CU system has several career development grants that focus on training the future workforce in niche areas, which do not have the capacity to meet the current demand from our CCTSI community, especially since translational research is multi-disciplinary. There are at least 4 reasons that justify the need for a CCTSI KL2 program. (1) There is high demand for the KL2 career development slots. Based on our four previous KL2 application cycles, over 30 applications are submitted for funding 5 slots. (2) For success as a CTR investigator, a comprehensive program that focuses on academic persistence and addresses many of the challenges of this goal is essential. Our KL2 program is uniquely modeled on achieving academic CTR persistence. (3) The CCTSI KL2 program provides a training opportunity for those trainees who do not fit the niche of other existing KL2 programs. For example, we currently have a pediatric urologist in the program that would not be eligible for any existing programs. (4) Our program is a catalyst for other K12 and K-awardee programs on campus. The CCTSI KL2 program, through our combined Career Development Seminars, will bring K Scholars from across campus to experience the benefits of peer mentoring, expand one another's networks of support for research and career advice and for career development in team science, leadership, entrepreneurship and dissemination and translation across the CTR spectrum. In this way, the CCTSI KL2 program will be leveraged for the benefit of all K-awardees on campus for a richer career development experience in key areas important to accelerate CTR in what would otherwise be a void.

B. PROGRAM PLAN

The Colorado CTSI KL2 program will support mentored career development of junior faculty engaged in clinical and translational research throughout our institutions prior to a first independent NIH (or equivalent) award. The main objective of the CCTSI KL2 program is ***to provide centralized training and mentoring oversight for junior clinical and translational researchers to overcome obstacles and increase their likelihood of obtaining independent success as researchers of the future***.

Our KL2 program will support 5 CCTSI KL2 scholars during each year for up to 3 years of support per individual. Additionally, to expand our reach and ensure that we have scholars in child health research, Children's Hospital Colorado (CHCO) will also fund 2 CHCO Junior Investigator Career Development Awardees who will attend our CCTSI KL2 activities. CCTSI-KL2 funding will enable protected time for research, mentoring for the scholar's research program, career development and coaching, infrastructure to support efficient conduct of research, and networking opportunities internally and externally to meet the career development needs and goals of scholars.

B.1. PROGRAM ADMINISTRATION

Our KL2 program leadership team is specifically designed to provide comprehensive oversight and mentoring across the spectrum of clinical and translational research (T0.5-T4; See Figure 3). Upon program entry, KL2 scholars will be assigned a primary KL2 program mentor according to their T1-T4 emphasis. Drs. Cara Wilson and Ellen Burnham will serve as Co-Directors of the KL2 program and will provide overall program oversight. The two have worked together in the KL2 program mentoring scholars for the past 4 years and have a cohesive, efficient and effective working relationship. Drs. Marc Moss and Lisa Cicutto will serve as Associate Directors. Leadership roles and responsibilities are described in Table 4. These 4 investigators have extensive expertise in career development and performance of research in basic/pre-clinical (Wilson), translational (Burnham), clinical (Moss), and community-based (Cicutto) research domains. They have long-standing and complementary expertise in mentoring junior faculty in CTR.

Figure 3: Program Administration's Experience Across the Translational Spectrum			
T0.5-1	**T2**	**T3**	**T4**
Cara Wilson			
	Ellen Burnham		
	Marc Moss		
		Lisa Cicutto	

Cara Wilson, MD will serve as the Principal Investigator and Co-Program Director for the Institutional Career Development (KL2) Core and also as the director for the Career Development Grant Review Program (Pre-K program; discussed below in Section B.3.3). Dr. Wilson is a Professor of Medicine with Tenure in the Division of Infectious Diseases at CU-D SOM, where she holds a secondary appointment in the Department of Immunology. Dr. Wilson has served as Vice Chair for Faculty Advancement for CU-D SOM for over 2 years and has developed and led programs focused on career development, promotion and advancement, diversity, gender equity, and leadership. Her R01-funded laboratory focuses on human immune response to HIV-1 infection and factors that drive HIV-1 pathogenesis, particularly in the gut mucosa. She also has extensive experience in designing and implementing HIV clinical trials, specifically studies of HIV-associated immune activation and immune-based therapies, through her involvement in the national AIDS Clinical Trials Group (ACTG). She has held numerous national leadership roles within the ACTG and currently serves as Chair of NIAID's AIDS Research Advisory Committee. She is a graduate faculty member in the Department of Immunology and serves as a research mentor to graduate students in Immunology, the Medical Scientist Training Program (MSTP), and the Biomedical Sciences Program (BSP). She received a K24 mentoring award and has mentored over 20 research trainees, ranging from pre-doctoral students to junior faculty.

Ellen Burnham, MD will serve as the other Co-Program Director for the Institutional Career Development (KL2) Core. Dr. Burnham is an Associate Professor of Medicine in the Division of Pulmonary Sciences & Critical Care, who has been involved in the KL2 program for the past 9 years. She will organize the monthly KL2 scholar seminars and quarterly activities with other existing Colorado K programs and awardees. Since 2006, Dr. Burnham has worked to further understanding and development of novel methods and techniques to improve mentoring. She served as our site PI for a U01 NIH-supported, multi-center mentor training trial[24] with Michael Fleming, MD, Northwestern CTSI; the curriculum of our KL2 and CO-Mentor program (described below) have been revised based on best practices identified by that study[24]. Dr. Burnham co-authored a position paper in JAMA[23] highlighting best mentoring practices of clinical and translational investigators and has been actively involved at the national level in mentorship and training. Dr. Burnham is currently chair of the American Thoracic Society's Women in Critical Care working group, where she is engaged in initiatives to enhance gender diversity. Dr. Burnham's research focuses on translational investigations in alcohol and substance abuse and critical illness, where she has mentored medical residents and junior faculty, both locally in Denver and at external sites, 3 of whom are funded by NIH-supported career development awards.

Marc Moss, MD served as Director of the CCTSI KL2 Program for the last 9 years and will remain as Associate Director to assist with transition to the new program leadership. He is the Roger S. Mitchell Professor of Medicine in the Division of Pulmonary Sciences & Critical Care and is Vice Chair of Clinical Research for the Department of Medicine. Dr. Moss has a longstanding interest in clinical and translational research involving ARDS, sepsis, and acute respiratory failure. He has held continuous NIH funding as a Principal Investigator for over 17 years. He has fostered a strong interest in the development of neuromuscular dysfunction in critically ill patients and its effect on diminished long-term outcomes. In response to a competitive RFA, Dr. Moss was awarded one of the new ARDS network sites (now called PETAL by the NHLBI), for which he is the co-PI of the protocol committee for the network's first clinical trial. Since returning to the University of Colorado Denver in 2006, he has been the primary mentor for 12 junior or mid-level investigators performing ARDS and critical care patient-oriented research. To support his mentoring efforts, Dr. Moss is the recipient of a K24 award from the NHLBI. Overall, these 12 trainees have received 8 grants in excess of $9,000,000 (including 4 NIH career development awards). Currently, he serves as the primary mentor on two K23 training awards: a prestigious NIA Beeson Award (a K23 equivalent), and a NIAAA K23 award. Over the last 5 years, his trainees have published 54 ATS abstracts, 47 original research articles, 17 review articles/editorials, and have 5 more submitted articles on which he was the senior or a co-author.

Lisa Cicutto, RN, ACNP(cert), PhD will serve as an Associate Director of the KL2 program. She directs the CCTSI's Translational Workforce Development (TWD) Core and the Clinical Science Graduate Program at CU-D, and is the Director of Community Outreach and Research at National Jewish Health. For the KL2 program, she will mentor and advise scholars that conduct research along the T3-T4 spectrum. Additionally, her knowledge of educational and career development opportunities within the CCTSI and University will be leveraged to benefit our KL2 as each scholar will meet with her to identify coursework and educational resources

to meet identified learning needs. Her research focuses on developing, evaluating, disseminating and implementing innovative best practice programs to improve the health of people living with lung conditions and co-existing morbidities by partnering with health care providers and individuals and families. Currently she holds

EPA and Colorado Department of Health funding to improve the health of those affected by lung conditions for those living in rural and environmental justice communities. She has held consistent funding as a Principal Investigator since 1998. Her passion is to work with, mentor and train future scientists to answer important patient/public health oriented questions that are subsequently translated to patients/people living in their communities. She has served in key roles and capacities for over 45 students related to their research projects and theses.

Table 4: KL2 Leadership Roles
Program Oversight
Attend monthly Leadership Advisory Council meetings
Scholar selection process: answer applicant questions, organize study section to review applications, serve as study section member, conduct interviews with finalists
Curriculum Oversight
Organize and participate in monthly KL2 Team Science, Leadership, Entrepreneurship Seminars
Advising and Mentoring: Review and update ICDP every 6 months, review manuscripts and grants, provide career development advice and support management of environmental pull factors
Diversity: Work to value diversity and to attract and maintain diverse KL2 Scholars
Ensure scholar is current with GCP, RCR and regulatory training
Faculty Review: Meet with mentors and mentee to ensure research productivity and, if necessary, resolve conflict
Program Evaluation: Meet with evaluation core every 6 months to review and apply data and feedback to enhance program

***National CTSA Consortium Involvement*.** Our Institutional Career Development (KL2) Core program leaders are involved at the national CTSA level and are collaborating with other CTSA KL2 programs.

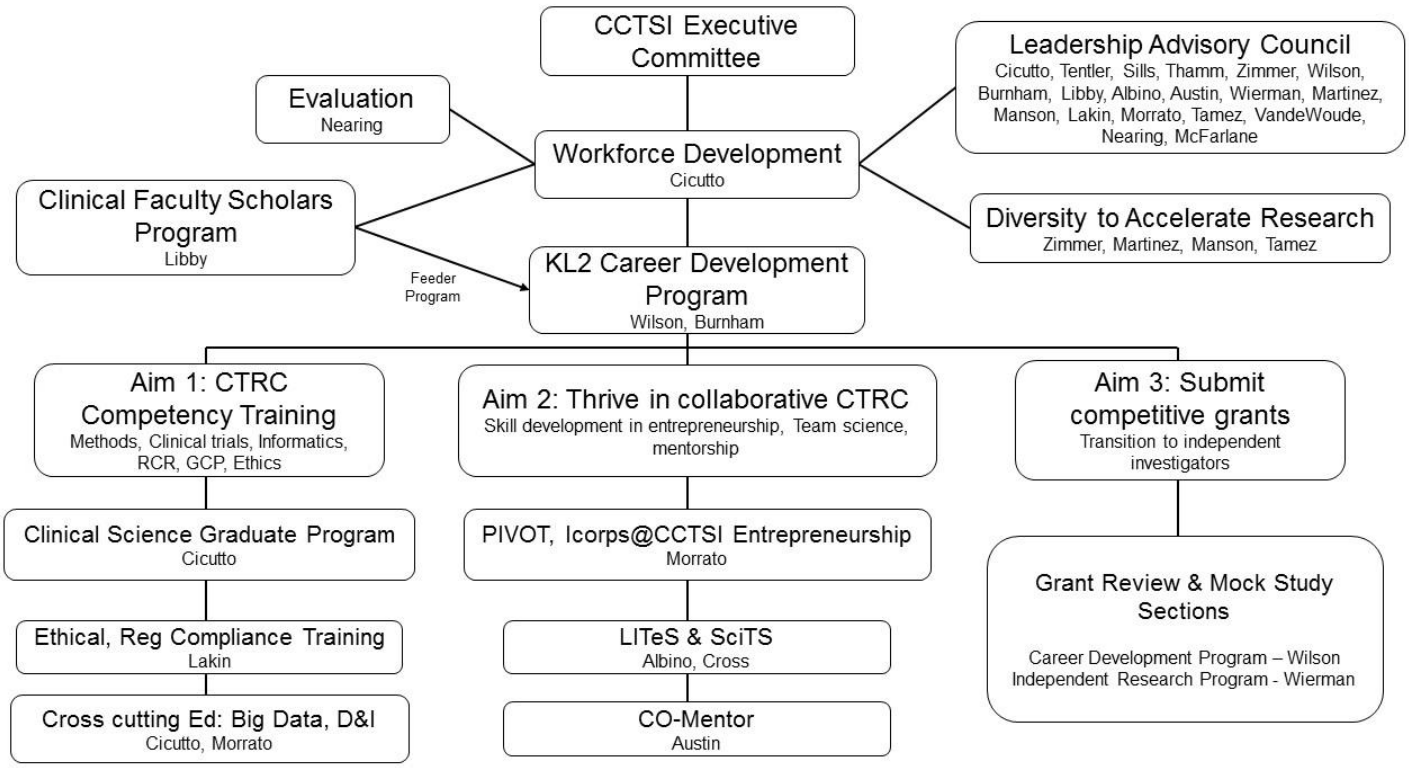
- 2010-11: Dr. Burnham served on CTSA Mentoring Working Group that produced two white papers.
- 2012-13: Dr. Burnham served as co-chairperson for poster sessions at CTSA annual conference.
- 2013-present: Drs. Moss and Cicutto (2016) Members, Workforce Development Task Force Workgroup
- 2013-present: Dr. Moss CTSA External Advisory Committee for Universities of Minnesota and Cincinnati
- 2014: Dr. Burnham, external advisor for Northwestern University's CTSA KL2 and TL1
- 2014-2015: Dr. Moss served as lead author for a series of articles published in *Clinical Translational Science* highlighting the CCTSI pipeline approach as an integrated approach to preparing the CTR Workforce
- 2016- present: Dr. Burnham, site PI for University of Pittsburgh Supplement Grant entitled "Unlock: Team Science" an online serious game strategy for teaching team science to KL2 scholars
- 2016-present: Drs. Moss and Cicutto, site PI for Univ. Southern California CTSI application in response to *U01 Individualized Development Plan Collaborative Innovation Award*

Galit Mankin, BA, MSW will be the Program Administrator for the KL2 Core. She has worked at CU-D since 1998 and for the last 8 years has served and will continue as Program Administrator for the Clinical Science Program. She has extensive experience developing relationships with trainees to provide guidance and advice for succeeding in training programs. Ms. Mankin works closely with Directors in coordinating recruitment efforts and selection of new scholars; tracking and reporting records for scholars; ensures compliance with NIH guidelines/regulations (including trainings for Good Clinical Practice and Responsible Conduct of Research); application of the xTrain system; and collecting and compiling annual progress reports.

The KL2 leadership team will be supported and advised by the larger infrastructure of the CCTSI's Workforce Development Program (See Organizational Chart, Figure 4). The **Leadership Advisory Council** will review the program curriculum, evaluative results and benchmarks, advise leadership for improvements related to enhanced integration within existing programs and infrastructure, and assist with advocacy to reduce and overcome environmental pull factors for CTR careers. The Leadership Advisory Council consists of all CCTSI Workforce Development educational program directors, leaders from the Graduate School, Office of Diversity and Outreach, School of Medicine's Office of Diversity, CCTSI Community Engagement, Regulatory and Evaluation leadership and will meet monthly (Third Tuesday afternoon of the month).

Program Leaders will be responsible for critical oversight (Table 4). A major role will be to advocate for institutional policies to alleviate environmental pull factors and to provide individualized coaching and advice to address environmental pull factors experienced by the scholar. Common pull factors include competing or conflicting demands, integration into projects and study teams, and promotion. Program leaders will attend monthly meetings of the Leadership Advisory Council.

Figure 4: Organizational Chart for KL2 Institutional Career Development Program



B.2. PROGRAM FACULTY

Our KL2 program has a large number of diverse, highly qualified, and successful CTR investigator mentors with outstanding research accomplishments and an exemplary record of training new investigators. Our KL2 program mandates that all KL2 applicants identify two co-mentors as part of their application. KL2 scholars choose their mentors based on common scientific areas of interest, previous mentoring success, and compatibility. A critical criterion of the selections process is the strength of the mentor/mentoring team proposed by the scholar. As a result of scholars selecting their research mentors, KL2 program faculty membership is fluid but all faculty must meet the following qualifications: (1) demonstrate a deep commitment to training junior investigators; (2) demonstrate a track record of excellence in mentoring junior investigators to become independently funded investigators; and (3) be actively involved in CTR with active research funding and productivity.

Should a potential applicant have difficulty identifying a mentor, the program director team will assist in identifying a qualified faculty member. Given the breadth of research across the CCTSI, we will be able to solicit necessary expertise from qualified faculty. There may be times when a mentor may change institutions or need to be removed from the program for various reasons such as conflicts of interests, personality clashes, lack of commitment, time and/or resources. Program directors will carefully monitor the evaluations of mentors in conjunction with Individual Career Development Plans (ICDP), and will arbitrate the removal of a mentor if necessary. Should this occur, program directors would help the KL2 scholar find an appropriate substitute.

Each KL2 Scholar will meet at least weekly with their research mentor(s) who will oversee progress according to their ICDP for research, training, and career development, including participation in the KL2 Program. Mentors will be responsible for ensuring the scholar adheres to practices of ethical, regulatory and responsible conduct of research (including IRB and IACUC approvals), maintains research-training certificates, and appropriately manages budgets. They will also assist in drafting and reviewing the scholar's grant proposals and be involved in the Independent Research and Career Development Awards Grant Review and Mock Study Section programs (See B. 3.3).

B.2.1. Mentor Training. While we have outstanding faculty to mentor our KL2 scholars, there are always areas for improvement and strengthening of mentorship skills. In an article examining the predictors of successful K to R transition, Yin et al.[1] identify *mentoring as the single most important contributor* to this success. Further, growing evidence suggests that successful mentoring involves formal training in mentorship and leadership[26, 28].

Based on this evidence and the call in the FOA for training to mentors to ensure successful scholar guidance by the mentor, all mentors will be *required* to attend two formal training programs:

a. Colorado Mentorship Program (CO-Mentor; see Section B.3.2.5.), for half-day quarterly sessions meeting over the course of a year.
b. Leadership for Innovative Team Science Program (LITeS; Described above in Infrastructure A.2). The LITeS program will ensure that the mentors cultivate a research environment that embraces team science and ensures the development of effective scientific collaborations for their KL2 scholar.

B.2.2. List of Faculty Mentors. Table 5 provides a representative example of disciplines and scientific fields, successes and experiences of a sample of our pool of possible KL2 mentors.

Table 5. Representative Mentors for KL2 Program

Mentor	Institution	Department or Training Program	Area of Research Expertise	Funding	Pre/post docs
Kristi Anseth, PhD	CU-B	Chemical & Biological Engineering	Development of synthetic extracellular mimics for cell culture	NSF/DMR, R21, HHMI	51/46
Kathleen Barnes, PhD	CU-D SOM	Biomedical Informatics & Personalized Medicine	Chronic complex lung diseases and inflammation	R01 x 4	8/30
John Belisle, PhD	CSU	Microbiology, Immunology, & Pathology	Metabolic response associated with Lyme disease and therapy	R21/R33, U01	17/52
Virginia Borges, MD	CU-D SOM	Medical Oncology	Breast cancer and high burden post treatment survivorship	R01, DOD x 2	14/8
Sean Colgan, PhD	CU-D SOM	Integrated Immunology	Inflammatory bowel disease	R01 x 2, T32, R37, VA	20/22
Dana Dabelea, MD, PhD	CU-D CSPH	Epidemiology & Biostatistics	Maternal diabetes and obesity during intrauterine life	UC4, CDC, R01 x 5, UG3, U01, R21	23/17
Gregory Downey, MD	CU-D NJH	Immunology & Microbiology	Chronic respiratory infections, injury	R01, R21, DOD x 2	40/28
Tasha Fingerlin, PhD	CU-D, NJH CSPH	Epidemiology & Biostatistics	Diabetes, chronic beryllium disease and schizophrenia	R01 x 2	13/0
Sonia Flores, PhD	UC-D SOM	Pulmonary Sciences & Critical Care Medicine	Role HIV proteins in endothelial cell activation and oxidative stress	U01, T34	1/16
Michael Ho, MD, PhD	UC-D SOM	Cardiology	Health Service Research	D4-Data driven Disc, VA x2, QUERI x 2	3/26
Fernando Holguin,MD	UC-D SOM	Pulmonary Sciences & Critical care	Epidemiological and translational asthma research	R01 x 3, P01, Univ of Pitts award	10/13
Allison Kempe, MD	UC-D SOM	Pediatrics, Health Outcomes	Community translational and outcomes research	R01 x 2, R18, U01	0/30
Wendy Kohrt, PhD	UC-D SOM	Geriatrics	Aging, metabolism, exercise	P50, DOD, R01, U01, R21 x 2	10/45
Elizabeth Kovacs, PhD	UC-D SOM	Surgery	Role of leukocytes and inflammatory mediators in tissue injury and repair	R01 x 2, R21, R24	0/21
Nancy Krebs, MD	UC-D SOM	Pediatrics	Zinc and trace mineral metabolism across the life cycle	U10, Bill and Melinda Gates Fnd x 2, T32, R01	10/26
Miguel Lanaspa Garcia, PhD	UC-D SOM	Medicine	Metabolic effects of fructose and sugar in disease	R01 x 2, K01, R03, VA Merit	8/10
Lisa Maier, MD	UC-D SOM, NJH	Occupational Medicine	Immunologic, genetic and genomic risk factors in diffuse lung disease	R01 x 6, UL1	0/9
Philippa Marrack, PhD	CU-D, NJH	Integrated Immunology	T cell receptors/autoimmunity	R01, HHMI, P01	11/42
Spero Manson, PhD	UC-D SOM	Community & Behavioral Health	American Indian health across the life span	U54 x 2, UL1, PCORI, U54,	0/75
Donald Rojas, PhD	CSU	Psychology	Neurodevelopmental disorders	R01 x 2, DOD	3/8
Dennis Roop, PhD	UC-D SOM	Dermatology	Mechanisms of skin diseases and skin cancer	R01 x 3, DEBRA, T32	8/7
Joseph Sakai, MD	CU-D SOM	Psychiatry	Neuroscience of addiction	R01, U01, R25	6/1

Nanette Santoro, MD	CU-D SOM	Ob Gyn	Clinical trials in reproduction in women with POS	R01 x 2, K12 x 2, R25, U01	0/36
David Schwartz, MD	CU-D SOM	Immunology & Microbiology	Effects of microbiome on the innate immune system	R01, R21, UH2/3, R25	0/9
Doug Seals, PhD	CU-B	Integ Physiol	Exercise physiology vascular aging	R01 x 3, R21 x 2	28/30
Robin Shandas, PhD	CU-D SOE	Bioengineering	Medical ultrasonics	R01 x 3, K24, T32	27/17
Kurt Stenmark, MD	CU-D SOM	Pediatrics	Pulm HTN / vascular biology	R01 x 5, P01, DOD, T32, R21	0/29
Jennifer Lapsley-Stevens, PhD	CU-D SOM	Physical Medicine & Rehabilitation	Minimally invasive total knee replacement vs tradition TKR	R01 x 2, R56, Va Merit, VA Spire	6/4
Andrew Thorburn, PhD	CU-D SOP	Pharmacology	Apoptosis in cancer development	R01 x 2, R21, K12, T32	10/12

B.3. PROPOSED CAREER DEVELOPMENT PROGRAM

All KL2 scholars will receive support for up to 3 years. During this time, they are coached, mentored and prepared to apply for either a career development award or an independent research grant (e.g. R01 or equivalent award) prior to the end of their second KL2 year. Based on our conceptual model of academic persistence developed by our colleagues Nearing and Manson[3, 6-7], our KL2 program encompasses **5 components** for a comprehensive training program as described in **Table 6**.

Table 6: Alignment between KL2 Program and Model of Persistence in CTR

KL2 Program Elements	Academic Persistence Factor Addressed
1. Individualized Career Development Plan (ICDP)	Formalized process to achieve individual's goals and milestones while leveraging CCTSI infrastructure
2. Mentorship	Provide effective mentorship and peer support to promote academic and social integration
3. Career Development Seminars	Advocating for self, working in teams, managing environmental pull factors and promoting academic and social integration into CTR
4. Immersion into CTR cultures	Provides meaningful research experiences and Promotes academic and social integration into CTR
5. Translation of CTR	Promotes academic and social integration into CTR

Individualized Career Develop-ment Plan (ICDP): ICDPs play a central role in the development of all scholars. All KL2 scholars will enter the program with 2 research mentors identified and establish individualized career development plans (ICDP) within a month of entering the program. The ICDP includes 4 areas with timetables: (1) Publications, (2) Grant applications, (3) Innovations leading to commercialization, and (4) Formalized activities to meet learning/career development goals. Program leaders (Wilson, Burnham, Moss, Cicutto) assigned to the individual scholar will meet with him/her to review ICDPs at least quarterly to monitor progress and attainment of milestones, evaluate career development goals, and the scholar's relationship with his/her mentors. Identified problems in attaining career goals or conflicts/unmet expectations will be addressed with the support of the KL2 program leader to promote resolution or to seek alternative approaches to ensure success for the scholar. Planning activities with timelines is an essential skill and necessary for navigating the complex landscape of CTR as an investigator. Early planning allows targeted activity for crucial steps necessary in preparing competitive grants and allows for the necessary revisions of grants required prior to submission. To hone our approaches and contribute to the literature, Drs. Cicutto and Moss are collaborating with the University of Southern California CTSI to identify best practices for integrating ICDPs in KL2 programs.

Translation of CTR. All KL2 scholars will attend and present their research at Translational Science, the national Clinical Research Training/Association for Clinical and Translational Science (ACRT/ACTS) meeting in Washington, DC. During this meeting KL2 scholars will present their work; learn important research concepts; engage in sessions relevant to career development (e.g. "The Power of Networking and People Skills," "Enhancing Rigor and Transparency in Translational Research"); and meet/ network with NIH program officers.

The remaining 5 components of the program (**Table 6**) will be described in detail below, as they are integrated the following **Specific Aims of our Program:**

B.3.1. Specific Aim 1: Optimize the provision of individualized competency-based training in translational research methodologies, clinical trials, data informatics, and ethical, regulatory and Good Clinical Practice principles.

Individualized Research Training: The CCTSI KL2 award provides $30,000 in funds yearly for scholars to obtain additional formalized training specific to the needs of each scholar. Most scholars require coursework to achieve the learning objectives of their ICDP and complete courses through the Clinical Science (CLSC) program (Described below in B 3.1.1). Within the first two months in the program, Dr. Lisa Cicutto, KL2 Associate Director and Director of the CLSC program, will meet with each scholar to navigate the educational opportunities available through the CCTSI/University to identify courses and develop an individualized course schedule for meeting his/her individual learning needs. KL2 scholars without previous training in clinical research methodology are expected to enroll in either the CLSC PhD or Master's Program. All KL2 Scholars *will complete Responsible Conduct of Research and Good Clinical Practice training described below in Section D.* Dr. Burnham provides two of these RCR seminars twice/yr, for KL2 scholars and others on campus, entitled "Responsibilities of Researchers in the Scientific Community" and "Mentor and Mentee Responsibilities."

B.3.1.1. As described above, we will target 4 areas of emphasis for skill development based on identified learning needs of our workforce that include team science, entrepreneurship, big data/informatics, and dissemination and implementation extending to community. Team science and entrepreneurship will be discussed below in Specific Aim 2 (B3.2). The CLSC has added several initiatives and opportunities for KL2 scholars to select from to meet their CTR phenotype and individual needs. The CLSC MSCS and PhD programs will add a track that focuses on ***Big data for discovery and decision support*** to prepare clinical-translational researchers to understand and take advantage of big data in the era of data driven discovery and health care. Scholars who choose to complete this program will complete required CLSC core courses and will focus and augment their training through directed electives such as: Big data – what is it and How do you use it, analytic methods (data wrangling, deep learning, natural language processing, P4 medicine (personalized, predictive, preventive, participatory) and Big data is a team sport. The CLSC and Data Science to Patient Value program (D2V) (described above A.2) will work collaboratively to offer coursework and provide mentorship. As an additional option for scholars, there is the collaborative multi-disciplinary ***Biomedical Data Science certificate*** program, consisting of 15 credit hours, beginning in 2018. Coursework will include Introduction to Biomedical Data Science, Introduction to Biocomputing, Practical Bioinformatics for Mining, Computational Methods Addressing Big Data Challenges, Power of Informatics to Advance Health, and an internship for application of learning. This collaborative effort includes medicine, cancer biology, biomedical and biotechnology, biochemistry molecular genetics, computational biology, and the Graduate School.

Working collaboratively with ACCORDS (Adult and Child Consortium for Health Outcomes Research) and D2V (See above Section A.2), the CLSC will extend offerings in ***Dissemination and implementation*** to include two new courses. *Mixed Methods in Dissemination and Implementation for Improved Health* will cover design, methods and analytical approaches for studies using both qualitative and quantitative methods. The second course, *Designing for Sustainability* will cover conceptual models/theories for sustained behavior change, interventional approaches, and leadership for change. Building on extending the skills for dissemination and implementation, is ***Community Engagement.*** Two CLSC courses available to scholars to build skills in community engaged research include CLSC 6211 *Immersion in Community Engagement* and CLSC 6669 *Community Engagement and Participatory Research: A seminar series.* A new initiative organized through the CLSC and the CCTSI Community Engagement & Research core is the integration of Community Research Liaisons into the monthly KL2 seminars and the availability of Liaisons to assist KL2 scholars to connect with the relevant community and patient-oriented organizations salient to the scholar's research.

B.3.1.2. Individual Research Studios will be conducted twice yearly to provide a structured and collaborative 90-minute roundtable discussion that brings together relevant research experts to help KL2 scholars with questions at any stage in the research process (see **Component C. Community and Collaboration**). Studios assist investigators with hypothesis generation and refinement, study design and methods, study conduct, analytical approaches, manuscript preparation, and translation to stakeholders. Each KL2 scholar will have a Research Studio to receive advice related to his/her specific strategic question. Studios have been successful in supporting grant development; 40% of participants have received funding for their grants.

B.3.1.3. Responsible Conduct of Research and Good Clinical Practice. Please refer to Section D below.

B.3.2. Specific Aim 2: Prepare our KL2 scholars to thrive in the new collaborative research environment by fostering skill development in team-based science, entrepreneurship, and mentorship.

B.3.2.1. KL2 Career Development Seminars are the core of the KL2 program. These are monthly 90 minute seminars held on the second Friday. At these meetings, two KL2 scholars will provide an update on their research and ICDP. Further, each scholar presents a specific obstacle or challenge that s/he is presently facing. After

presenting career development progress and challenge(s), feedback from the group on progress and limitations will be solicited. These sessions will facilitate identification of issues that may impede the success of KL2 scholars and address them in a timely fashion before they become insurmountable hurdles. KL2 directors are particularly experienced in finding solutions for challenges that include threats to protected time for research, conflicts in mentee-mentor communication and expectations, and operational issues impeding successful completion of research (i.e. personnel issues). KL2 peers may offer additional insights and solutions and learn from challenges encountered by others. The seminars can also inform program directors of the need for additional remediation to ensure scholar success, such as additional oversight and mentoring. When necessary, KL2 directors will meet with a KL2 scholar and mentors to directly address concerns. KL2 program directors will also provide other support for scholars including reviewing grant applications and manuscripts, providing career development advice, assisting scholars with networking both at the University and national levels, and providing support when negotiating for new positions.

Quarterly, other K awardees at CU-D and CCTSI affiliates will be invited to join CCTSI KL2 scholars for career development seminars germane to all K scholars. Previous larger K awardee group seminars were attended by over 25 additional K awardees and included topics such as review and critique of Specific Aims pages, writing Mentor Support letters for career development awards, and use of social media to promote one's research. In these seminars, CCTSI KL2 scholars and other K scholars can expand both their knowledge base, as well as grow their local research network across the university system, as well as engage in peer-mentoring opportunities. Although traditional dyadic mentoring with faculty is the dominant model, there is increasing recognition that the sharing of knowledge, skills, and experiences among peers contributes to the career development of junior faculty. Benefits of peer-mentoring include increased peer interaction and collegiality and longer-term tangible outcomes, such as manuscripts and grants that come from collaborations.[29-31]

B.3.2.2. Skills in Entrepreneurship have been identified by Chancellor Elliman as essential elements for CU-D AMC's clinical and translational enterprise and will be the focus of our CCTSI optional component, Innovation Ecosystem (**Component H2. Innovation Ecosystem**). The KL2 program will capitalize on PIVOT's career development opportunities. KL2 scholars will have the following programs available to them: **I-Corps@CCTSI** is a team-based series of workshops that guide teams through the early stages of customer discovery and an online course addressing the different commercialization pathways for drugs, devices, diagnostics and tools. In addition, the CU-D Graduate School through their **NIH funded BEST program** provides two courses related to commercialization in the life sciences: *Introduction to Life Science Commercialization* and *The Legal and Regulatory Environment of Life Science Innovation*. The first course familiarizes scholars with fundamentals of life science technology commercialization including drugs, devices, diagnostics, healthcare IT and platform applications, and the second course covers regulatory and legal aspects of commercialization for life science technologies. KL2 scholars with an interest in product development or commercialization of an idea will be guided to these courses. In addition **Engagement between Academics and Industry** is a trainee-led Academia-Industry Alliance, with CCTSI support, which holds an annual Rocky Mountain Biotechnology Symposium and quarterly Brews and Biotech Happy Hours to forge relationships among industry, faculty, and trainees. KL2 trainees will attend the annual symposium and be encouraged to attend the quarterly Biotech Happy Hours. Last year's symposium was highly successful with over 300 faculty and trainees and 35 bio-technology companies in attendance. Presentation topics included understanding and working with industry, new developments and innovations, and networking. Quarterly Biotech Happy Hours will provide an excellent opportunity for KL2 scholars to network, have ongoing dialogue with industry and coordinate externships.

B.3.2.3. Immersion into CTR Cultures: Opportunities for Externships will provide KL2 scholars with opportunities to immerse themselves into the private enterprise world in which to learn the perspectives and experiences of other sectors related to CTR. This knowledge and insight are important for developing relationships, forging collaborations, building trust, speaking their language and addressing meaningful research questions. We have developed the following opportunities for externships, ranging in duration from weeks to months, which could be taken for graduate credits. Table 7 provides externship examples. Externships will be arranged by Program Directors for interested KL2 scholars.

Table 7: Examples of Possible Externships for KL2 Scholars

Bio Tech Research, Development, and Commercialization	
Biodesix	Personalized non-invasive oncology diagnostics
Corgenix	Diagnostic tests and instrumentation for hemostasis, autoimmune and vascular disease

Flagship Biosciences	Tissue analysis platform for biomarkers and diagnostics
Medtronic	Medical technology, devices and services
GE Healthcare Dharmacon	Production of molecular tools related to gene editing & expression, RNA interference, and custom RNA synthesis
Microtek	Development and manufacturing related to microencapsulation and phase changes materials (PCMs)
Empirical Tech	Consulting, testing, and manufacturing services related to medical device development and production
Sharklet Technologies	Shark-inspired technology to inhibit microbial growth purely based off of structural pattern
Terumo BCT	Medical devices for blood component, therapeutic aphaeresis, and cellular technologies
Trans1	Medical device for minimally invasive spinal surgery
Bio Tech Support Services	
3D Systems	Manufactures and provides 3D printing products and services
Front Range Biological Safety Association	Teaches and promote knowledge of biological safety principles
Technical Safety Services	Testing, calibration, and certification of equipment for compliance with regulatory standards
Health Information Technology	
Health Language	Software development for clinical documentation, data quality and interoperability
The Breakaway Group	Changing the way health care providers use electronic health record (EHR) technology
Community Organizations	
Community-Campus Partnership	Partnerships between University/AMC and Aurora community to improve health and economic well-being
Rcky Mtn Poison & Drug Center	Public health services and outreach. Conducting research related to the reduction of toxicity, injury and disease.
Stapleton 2040	Advancing community health through community-based research projects and policies

B.3.2.4. Science of Team Science (SciTS*)* and Leadership for Innovative Team Science (LITeS). These two programs will provide a curriculum to catalyze and develop interdisciplinary teams. This new aspect of our KL2 program is based on research conducted by colleagues, Libby and Abman[25], that identified specific challenges posed by team science within the context of academic researcher, which requires specific training in leadership and team science. Our series of workshops will focus on learning how to build productive and effective teams and to understand the value of team building. Specific concepts discussed will include emotional intelligence, leadership qualities, communication skills, and the importance of diversity of skills in highly functioning teams. This initiative will be offered to KL2 scholars as a series of workshops held during their monthly Career Development Seminars. These workshops are scaled up from activities first developed and evaluated at Colorado State University's (CSU) SciTS and the CCTSI's LITeS[26]. Jeni Cross, PhD (CSU) and Judith Albino, PhD (LITeS, CU-D; **See Biosketches, Component C. Community and Collaboration**) are lead faculty directing these offerings with the support of additional workshop faculty. This new adapted integrated curriculum for our KL2 scholars will be referred to as **LITeS-Jr.** Based on early experiences, our Evaluation Core observed that leadership training empowered junior investigators to thrive as independent CTR investigators and therefore will be provided to all KL2 Scholars through these programs.

B.3.2.5. Mentorship training: Mentorship positively influences academic productivity, feelings of self-efficacy, job satisfaction, and career development[24],[32-35] and thus is core to our model of CTR persistence. Mentees with influential and sustained research mentoring are more likely to remain in research, publish and disseminate their research, become principal investigators, and mentor others.[36] Formalized efforts to improve the skills of our KL2 mentors include the requirement of mentors to complete the LITeS program (described above, see A.2 Infrastructure) and to complete a mentoring program, CO-Mentor with their mentee. Members of our team are national leaders in the area of the science of mentoring. One of our co-directors (Dr. Burnham) was a co-author on the mentoring commentary published in JAMA and several other mentoring related articles.[21-24]

Studies show mentors and mentees benefit from a formal, structured training program to enhance the mentor-mentee relationship.[37-39] We created a novel mentoring program, **CO-Mentor**, during the last funding period that includes both the mentor and the mentee. All KL2 scholars and their mentors will be required to complete the program. Gregory Austin, MD, MPH is the Director, with Dr. Anne Libby serving as Associate Director. CO-Mentor's aims are to: (1) develop skills and behaviors consistent with effective mentoring relationships; (2) enhance the specific mentor-mentee relationship in the process; and (3) build a network of trained mentors and

mentees who could model these practices for others, leading to a sustainable culture of mentoring at CCTSI-affiliated institutions. CO-Mentor consists of four half-day sessions, occurring approximately every 7 weeks. Session 1 will focus on career mapping skills and interpersonal communication skills. The CVs of mentors and mentees are reviewed to highlight whether an individual's career goals are appropriately reflected. These interactive self-knowledge and communication skill-building activities are the foundation for enhancing mentoring outcomes. Session 2 will be split into two halves. During the first half, the focus is on understanding financial aspects of an academic career: negotiating percent effort for research, education, clinical, and administration; managing project budgets; and salary support/funding portfolio. The second half of the session is the only time mentors and mentees are separated. During a discussion on "Creating and Managing Your Personal Board of Directors," mentees will focus on how to build a comprehensive mentoring team. Attention is focused on how mentees can optimize these relationships by knowing their needs and communicating expectations to their mentors. Separately, mentors will discuss techniques to give and receive feedback from mentees. Before the next session, mentees will review mentoring team gaps with their mentors and formulate a plan to fill identified gaps. Also, participants will complete Values Clarification/Goal Setting Worksheets and craft a brief personal narrative that elaborates the rationale, values, and passion for their career path. Session 3 will focus on improving goal setting skills using reflection on personal strengths and values, as well as effectively using peers and mentors to help design, implement, and track achievements and goals. Before the next session, mentees revise the personal narrative and review with their mentor. Session 4 will have participants applying a conceptual framework for making personal work choices that promote academic growth and persistence. Time management strategies will be reviewed in the context of achieving work goals, and an interactive network exercise is used to reinforce networking skills important in building professional relationships. Additionally, we will have an interactive presentation on writing effective letters of support.

CO-Mentor has consistently achieved high levels of participant satisfaction from mentors and mentees. Mentees reported benefits in the following areas: 95% agreed/strongly agreed that they had greater clarity regarding their career and development needs and 91% of mentees were more confident that they could successfully establish mutually-agreed upon goals and expectations with a mentor. Mentors reported the most significant gains in the following areas: providing coaching ($p=0.001$), developing and reviewing a personal career development plan ($p=0.002$), identifying strengths and gaps in the mentoring team ($p=0.004$), and intentionally working to achieve a satisfactory work-life balance ($p=0.001$). Of the mentors, 26% were assistant professors, 45% were associate professors, and 29% were full professors. Of the mentees, 59% were assistant professors or instructors while 41% were MD or PhD postdoctoral fellows. By ensuring our KL2 scholar-mentor dyads have free access to the CO-Mentor, our CCTSI is supporting the growth of a solid mentor-mentee relationship critical to mentee success.

B.3.2.6. Develop, Demonstrate and Disseminate. Based on the success and evaluation of our CO-Mentor and LITeS programs[26], both have gained interest of other CTSA Hubs wishing to implement similar programs. Thus, we will focus on developing curriculum and program delivery supports for implementation, demonstrating that these materials and model for training future implementers are effective and then disseminating these to other CTSA hubs and academic CTR settings. Dr. Austin has been collaborating with and traveled to the University of Miami CTSA (See Letter of Support) to meet with their CTSA and Career Development leadership to discuss piloting, testing, and implementing CO-Mentor. Similarly, Dr. Judith Albino, Director of LITeS, has visited with leaders at CTSAs in Cincinnati and Minnesota (see Letters of Support). Our dissemination and implementation model will involve a combination of online materials and on-site instruction. Dissemination and implementation will occur over 6 phases:

Phase 1 (Develop): From 2018-2019, develop program kit that contains the necessary materials/resources to deliver the program, such as a curriculum manual, trainer's manual, slide decks, workbook, etc.;

Phase 2 (Develop-Demonstrate): From 2018-2019, understand the readiness of external CTSAs for implementing (CO-Mentor or LITeS) by conducting a readiness survey and having future implementers complete the respective program, CO-Mentor or LITeS;

Phase 3 (Demonstrate): During 2019, provide train the trainer program to external CTSAs involved in piloting to build the necessary skills and to address readiness issues identified for successful implementation;

Phase 4 (Demonstrate): From 2019-early 2021, pilot, evaluate and refine materials based on implementation experiences in piloting sites;

Phase 5 (Disseminate): Based on readiness work and pilot implementation experience, develop a dissemination plan for broader scalability, and

Phase 6 (Disseminate): Starting in 2021, disseminate CO-Mentor and LITeS to interested national CTSA Hubs and other academic health centers. For detail on the evaluative approach see Section B.4 Program Evaluation.

B.3.3. Specific Aim 3: Assure that KL2 scholars submit competitive grant applications to transition to independent investigators.

There is recognition and great appreciation for the difficulty that many early stage CTR investigators experience in securing grants. It is likely that this disappointment and frustration contribute to burnout, and lead to many would-be CTR leaders discontinuing their pursuit of CTR careers. This is costly to the individual and society. Therefore we have dedicated efforts to work with KL2 scholars to learn skills for preparation of the most competitive grant applications. Given the length of time between grant submission and funding, early planning and preparation is essential. Our KL2 scholars will begin addressing future research opportunities within their first month and this planning is formalized in their ICDP. Two types of mock grant review and study sections programs will be available and held corresponding to NIH deadlines: one for career development awards and the other for independent research awards. These programs support success of K scholars in receiving their first independent research funding by providing pre-review of the application, topic expert grant reviews and participation in a mock study section to elucidate the peer review process in an effort to improve the quality and competitiveness of applications. This type of program is important, as up to 30% of K awardees do not progress to even applying for an R type award nationally[40]. Preparation of a competitive application is critical to the future success of junior faculty to advance within the academic pipeline.

Cara Wilson, MD, will direct the **Career Development Award Grant Review (Pre-K)** and Mock Study Section, while Margaret Wierman, MD, will direct the **Independent Research Award Grant Review (K to R)** and Mock Study Section. Both the Career Development and Independent Research Award Grant Review and Mock Study Sections are held in the two-month interval before NIH study section deadlines to provide assessment and input to allow time for application revisions. Each program will function in a parallel process. The first element of the process is to submit a letter of intent (LOI), in essence a Specific Aims page. Drs. Wierman or Wilson read each submitted LOI and then provide timely input into the organization of the proposed project along with commentary on clarity in design and outcome measures as the application is developed prior to full review. Expert reviewers are solicited across the CU, CSU, and CCTSI affiliates based on the LOI topics for full application review. What sets our process apart from others is that applicants, mentors (if appropriate) and reviewers all attend the mock study section for the corresponding grant review and mock study section. The study section is organized like a standing NIH panel, apart from the fact that the applicants (and mentors, if applicable) are present for the discussion and ALL submissions are discussed. After proposals are reviewed, the chair requests comments/insights from participants and the applicant is permitted to respond to criticisms, or ask questions. The spectrum of scientific areas and approaches of applications allows the chair and core members to reflect on strengths and weaknesses across all applications and to educate all on common themes of style, language and approach. Reviewers include both senior investigators with current membership on NIH or similar grant panels and more junior reviewers who benefit from participating in the review process and communicating their reviews in a group setting. Providing these structured opportunities for junior faculty recently funded to participate in a formal study section prepares them for participation at a national level.

The Career Development (Pre-K) Program has reviewed 77 applications since 2014. Our overall applicant success rate of 48% is higher than the national average of 30% for K awards[40-41] and more than $12M dollars in grant support has been awarded. The Independent Research Award (K to R) program reviews 7-10 applications per cycle. Two-thirds of submitted applications are R01 submissions but any independent research type application may be submitted. Of the reviewed R01 applications, *16% were funded within one year while 25% were funded within 2 years.* Importantly, *over 46% of participants received some type of independent research funding within a year of program participation with grants totaling $67 million.* Our success rates demonstrate the effectiveness of the program, which exceeds the national rate of 15% for the same time frame.[40] Qualitative feedback from participants, mentors and reviewers is overwhelmingly positive.

Vignette: The experience was invaluable! I learned so much about the review process by watching the reviewers introduce a grant and then discuss …I also very much appreciated and needed all of the feedback from reviewers on how to improve my grant. I loved that I was allowed to be present so that I could hear the discussion as well as ask for clarification! Again, such a wonderful learning experience. I also learned a great deal from listening to reviewers' comments on the other proposals … as sometimes I made the same errors.

Collaboration and Dissemination: Our goals for the newly proposed KL2 funding cycle are to streamline and improve the review process, expand our reviewer pool to meet the needs of increased topic diversity of applications, and to create a community of learning with other CTSAs in our region. Our first outreach will be to University of Utah to disseminate and share our expertise and organizational processes and to learn from and leverage collective resources. Dr. Wierman will be part of Utah's CTSA External Advisory Committee for their KL2 program and of their K to R/Independent Research Award review committee and will help implement the program in Utah during the next funding cycle. We will be combining reviewer lists and will serve as external reviewers for one another's applications. Additionally, we are interested in identifying strategies for improvement and demonstrating their benefits to enrich the experience and competitiveness of our scholars. **Experimental approach**- Specifically, we will demonstrate whether or not there is added value to providing a face-to-face feedback/coaching session following mock study section and grant reviews compared to written feedback only. Applicants will be randomized to receive the added element of face-to-face feedback/ coaching compared to written feedback. To assess the comparative effectiveness of each approach, we will compare submission and success rates controlling for grant type and number of times they participated.

B.4. PROGRAM EVALUATION

The CTR persistence model[7] presents strategies to be completed at programmatic and institutional levels to support persistence decisions among early career CTR investigators. The strategies include: 1) creating a seamless pipeline by forming strategic partnerships to achieve continuity of support for scholars and collective impact in relation to expanding (i.e., diversifying) the CTR workforce; 2) providing meaningful research opportunities to support identity formation as a scientist and sustain motivation to pursue and persist in CTR careers; 3) fostering an environment for effective mentorship and peer support to promote academic and social integration; 4) advocating for institutional policies to alleviate environmental pull factors; and 5) supporting program evaluation – particularly, the use of evaluation data to guide quality and process improvement and the examination of longitudinal outcomes. By combining institutional policies that promote a culture and climate for diversity with quality, evidence-based programs and integrated networks of support, the CCTSI Workforce Development Core will create the environment necessary for diverse scholars to progress successfully and efficiently through the pipeline to achieve NIH's vision of a robust CTR workforce. As our evaluation is aligned with our model for CTR persistence and the five recommended strategies, please review **Table 8** displaying the five programmatic recommendations, associated components and corresponding outcomes and metrics.

Table 8: Evaluative Framework Aligned with Model for CTR Persistence for KL2 Program

	KL2 Program Components	Key Metrics and Outcomes
Seamless Pipeline	• Leadership Advisory Council comprised of pipeline program directors will ensure needs of scholars are met by providing integrated supports across the career trajectory and during vulnerable transitions and will attract and retain diverse students • Individualized Career Development Plans and annual progress monitoring • Diverse array of training opportunities, resources, and services offered to meet complex academic and career development needs across pipeline	• Expanded pool of well-qualified applicants from diverse backgrounds • KL2 scholars persistent in CTR: # and % (disaggregated by gender, race, ethnicity and disadvantaged social/economic status) • KL2 scholars are competent in CTR: consistently report high satisfaction with preparation and high levels of confidence for CTR competencies • KL2 scholars are committed to pursuing CTR careers • KL2 scholars demonstrate independent funding (seamless transition from K to R and "R-like" operating grants) • KL2 scholars are productive scientists indicated by bibliometric analyses
Meaningful (Impactful) Research	• Immersion into CTR cultures that include mentored research projects across the study lifespan and available externships with community and industry. • Opportunities to share research vision and products/ accomplishments (KL2 seminars, participation in professional and CTR meetings and engagement with local, national networks) • Integration with Community Engagement Core (connection to training programs) to support stakeholder engagement • Expanded training to foster team science, dissemination and implementation, entrepreneurship	• Self-determination[42], confidence in CTR abilities and competence as a CTR investigator (Validated Clinical Research Appraisal Tool[43]) • Enhanced intrinsic motivation that sustains emotional energy and investment in work (Validated Inner Strength Scale[44]) • Identity formation as CTR investigator • Documented completion of required ethical and regulatory training (RCR, GCP) • Increased research collaborations that enhance rigor, relevance of research, job satisfaction (quality of work environment) and connectedness • Engaged in team science • Enhanced impact of research products and satisfaction with CTR as a career
Effective Mentorship and Peer Support	• KL2 scholar mentoring team to provide the cross-cutting functions of effective mentorship support[5] • Mentor-mentee dyad participation in CO-Mentor program to optimize productivity • Monthly KL2 Career Development seminars provide both faculty and peer mentorship to scholars • Regular ICDP review	• KL2 scholars consistently report effective mentorship: 1) established strategic goals; 2) devised pathways to success (including alternative strategies when challenges emerged); 3) accessed necessary resources and services; 4) developed professional competencies, including skills for managing work environment; and, 5) received social-emotional support (Validated Mentoring Competency Assessment[45]) • KL2 scholars are socially integrated into CTR community- strong connection to faculty and peers

Institutional Policies to Address/ Ameliorate Environmental Pulls	• Availability of CCTSI-supported Micro Grants (to off-set costs of research resources and services) and pilot grant funding • KL2 salary support and mentors who protect scholars' research time • Promotion and tenure criteria supportive of team science • CO-Mentor program completion to help KL2 scholars navigate competing demands that might detract from career goals and to advocate for self to manage environmental pulls • Leadership Advisory Council to make advocate and make recommendations for policies to ameliorate pull factors	• Maintenance of Micro Grants as a committed resource for early career investigators; including distribution of funding to early stage investigators • Maintenance of pilot grants program, including specific pilot grants available for mentored junior investigators and those wishing to start a new team science endeavor; documented implementation and outcomes of program • Protected time for research • Establishment of promotion and tenure criteria supportive of engagement in team science (e.g., review of and documented changes to SOM promotion and tenure criteria)
Program Evaluation	• Comprehensive, with institution-, program- and scholar-level outcomes delineated • Theory-driven, relying on validated instruments • Mixed-methods, longitudinal approach • Analytical approach situates KL2 within the context of the comprehensive, holistic evaluation of the CCTSI and associated pillars/components	• At least semi-annual reporting of common metrics • Robust program evaluation – that examines program implementation and effectiveness holistically – provides important contextual information to help pin-point effective strategies and appropriate targets for "turning the curve" • Continuous quality and process improvement • Enhanced program effectiveness resultant of needs identified through evaluative efforts

To evaluate our pilot project for developing, demonstrating and disseminating CO-Mentor and LITeS before scalability at a national level, the Evaluation Core will engage early-adopting sites in a study to determine (1) readiness to implement each program with fidelity, (2) the supports needed to achieve fidelity of implementation at early-adopting sites, and (3) reproducibility of program outcomes across implementation sites. Evaluation questions and data sources/methods are outlined below in Table 9.

Table 9: Evaluation of Piloting of CO-Mentor and LITeS

Domain	Study Question	Data sources/ Methods
Implementation Feasibility	1. To what extent are all components of the program model feasible to implement at other CTSA hubs? 2. What level of program fidelity is achieved at newly-adopting CTSA hubs? 3. What resources are necessary to support the implementation of the program model with fidelity at other CTSA hubs?	• Thematic analysis of focus group and/or key informant interview data with trainers, key administrators, local evaluators • Fidelity of implementation scores (collected with observational protocol completed by expert reviewer from CCTSI ETCDC) • Notes taken during site visits, training session observations • Debriefing sessions with expert reviewers
Program Outcomes	4. What are key stakeholders' attitudes and beliefs about the effectiveness of the program? 5. How generalizable are program outcomes reported using standardized evaluation instruments disseminated with each program model?	• Thematic analysis of focus group and key informant interview data • Results of standardized evaluation instruments
Dissemination	6. What modifications need to be made to support national dissemination? 7. What are the implications for standardizing and replicating the program to expand its reach and achieve reproducible results?	• Thematic analysis of focus group and key informant interview data • Notes taken during site visits, observations • Evaluative synopsis across methods and associated analyses

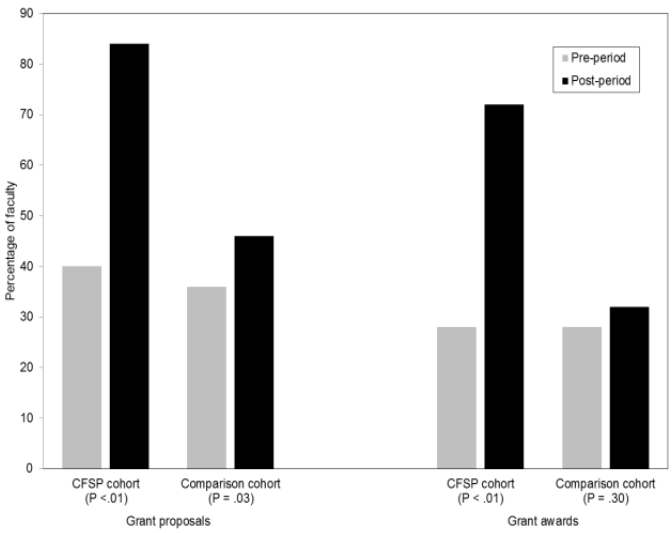
The CCTSI Evaluation Core will implement the national dissemination-implementation study in collaboration with evaluators associated with each implementation site. The CCTSI Evaluation Core will develop an observational protocol that will be used by original program developers to observe program delivery at early-adopting sites and score the fidelity of program implementation. Other evaluation instruments that will be packaged for dissemination with the program model include:

- Session-specific formative feedback surveys that reflect/are responsive to the scope and sequence of the curriculum;
- Validated **CO-Mentor** survey designed as a pre/post assessment
- **LITeS:** End-of-program outcome survey (featuring post-then pre item design);
- Longitudinal follow-up surveys
- **LITeS:** Evaluation framework that operationalizes stages of leadership competency and mastery for assessing the duration of program effects at each site.

B.5. CANDIDATES / SCHOLARS

***B.5.1 Applicant Pool**:* CU-D has 29 active postdoctoral T32 training programs that provide foundational training for many of our excellent KL2 applicants. Our T32 programs are among the best in the nation, with six of these programs (Behavioral Pharmacogenetics of Drug and Alcohol Abuse; Gastrointestinal Diseases; Renal and Electrolyte Disease and Hypertension; Developmental Psychopathology; Psychobiology and Behavior; Pulmonary Disease, Respiration and Circulation during Hypoxia; and Perinatal Biology and Medicine) receiving funding for more than 30 consecutive years. Additional KL2 applicants are newly recruited junior faculty to our institution from top-tier academic institutions. A measure of the competitiveness and diversity of our applicant pool is the number of applications that are received from qualified trainees. After 4 cycles of competition we consistently receive more than 30 KL2 applications with funding rates ranging from 16-19%. (Refer to **Table 1** above).

An excellent "feeder" pool of multi-disciplinary applicants for the KL2 program is the **Clinical Faculty Scholars Program (CFSP**), a two-year mentored research fellowship for early-career faculty members pursuing independent funding in health outcomes and clinical services research. Participating disciplines include medicine, pediatrics, surgery, emergency medicine, epidemiology, law, decision sciences, nursing, and medical anthropology. Program goals are achieving successful extramural grant awards, publications in peer-reviewed journals, establishment of local mentorship teams, preparation for promotion via academic dossiers, and acquisition of research and career development skills. CFSP participants work towards a primary goal of submitting a research career development award. Each CFSP participant is assigned a primary CFSP mentor and a biostatistician, develops an ICDP and receives regular individual mentorship from 4 experienced senior researchers in clinical epidemiology, health services research, biostatistics, and qualitative methods. KL2 applications from CFSP graduates are characterized by their superior preparation and are therefore primed for KL2 award success. *30% of our KL2 scholars have successfully completed the CFSP.*



An evaluation of the CFSP, published in *Academic Medicine*[46], demonstrates that participants prepare, submit and attain grants more often than their matched comparison group. Compared to a matched group of faculty based on grant dollars, CFSP participants had significantly increased proposals and awards; this effect is evident by the end of the program and persists over time. It also demonstrated that CFSP participants are significantly more likely than comparison faculty to resubmit proposals after rejection. A second manuscript about the "mechanism of action" of the program's success is submitted. These data (unpublished) suggest a significant impact on participant self-efficacy, whereby participants normalize experiences, including rejection, and learn strategies to pursue a research career.

***B.5.2 Eligibility, recruitment, and selection of KL2 scholars**:* All KL2 program candidates must have a) a research or health-professional doctoral degree, b) a faculty appointment and c) be actively engaged in CTR. Every 24-36 months, requests for applications will be distributed by email and announced on our website to the entire CCTSI community, including affiliate hospitals, CU-B and CSU, at least 8 weeks before the application deadline. Applicants will be required to identify 2 co-mentors who are located at a CCTSI affiliated institution. Two common co-mentoring models are described below but other models may be acceptable.

1. Clinical/Methodological Mentors: Scholars may require co-mentors with different research skills and areas of expertise. For example, a translational project may require one epidemiology mentor who is adept in study design while the second mentor has expertise in the processing and analysis of samples obtained from human subjects. This model encourages and has resulted in new collaborations between senior mentors.

2. Senior/Junior Mentors: In this model, one senior mentor provides extensive experience in the scholar's research area and networking opportunities, while the second, junior mentor, is a mid-level investigator with independent funding yet less research experience. The junior investigator provides daily, hands-on mentoring,

while the senior mentor provides guidance on broader research goals and career development issues. This system builds mentoring skills for the junior mentor, thereby expanding the pool of future potential mentors.

B.5.3 Application process: Applications will be submitted through our on-line CCTSI submission website to facilitate distribution of applications to reviewers. Instructions to assist with application completion and contact information are posted on our website. Dr. Burnham will serve as program officer, fielding questions regarding such issues as their suitability, mentoring strategy, and contents of the career development plan. Applicants will submit a 10-page grant proposal (similar to Independent K Award applications) with the following sections: prior research experience, career development plan, and a research plan including study design, statistical methods and feasibility sections. Letters of support from their research co-mentors are required describing their commitment to the applicant and their specific mentorship plan. *The division chief or department chair must provide a letter of support stating that at least 75% (9 calendar months) of the full-professional effort of the applicant will be protected for research career activities and $25,000 per year for research related activities will be provided for the duration of the award*.

B.5.4 Review process: Members of the Applicant Review Committee will represent the broad T0.5 to T4 CTR spectrum. After eliminating applicant-reviewer conflicts of interest, all reviewers electronically receive assigned proposals with KL2 review criteria that include the potential of the applicant, necessity of additional mentoring in the success of the applicant, the likelihood that the project proposed will advance clinical and translational science, and the likelihood that CCTSI KL2 program will contribute to attaining successful independent funding prior to the end of the KL2 award. Each proposal is evaluated by at least 2 reviewers with expertise in the area of the applicant's science and in career development awards. Using the 9 point NIH scale, the reviewer assigns an overall score and individual component scores in five areas: candidate, career development plan, research plan, mentors and mentoring plan, environment and institutional commitment. After ranking submitted reviews, an in-person study section with all reviewers will be held to discuss the top~50% of applications and to re-rank applications. In the second stage of our review process, top scoring applicants are invited for an interview with KL2 program and CCTSI leadership to review outline expectations of awardees prior to the award's disbursement. The interview allows program leadership to assess and confirm mentor commitment, resources to be provided by the mentor and sponsoring department, timeline of milestones and the process to monitor progress. All applicants (funded and unfunded) receive written review of their KL2 application. A new initiative, starting in 2018 involves collaborating and coordinating KL2 grant reviews with the University of Utah CTSA. We will share reviewers for 20% of applications that will (1) increase and diversify the pool of qualified reviewers in methodological expertise, (2) bring in external expertise, and (3) promote economies of scale by collaborating and coordinating grant reviews with the Utah CTSA.

B.6. INSTITUTIONAL ENVIRONMENT AND COMMITMENT TO THE PROGRAM

The CCTSI, as a statewide collective community of academic hospitals, universities, community partners and their faculty and staff, are deeply committed to rigorous training of the future generation of investigators and the development of outstanding investigative teams and will provide substantial support to the CTSI KL2 Program and Scholars. Described below are commitments to the KL2 program and scholars:

Protected time: At the heart of the KL2 award, funding to protect 75% of the scholar's time to devote to training and the proposed research will be assured (50% for surgical or specialty-focused applicants). All scholars will have written approval from their department chairs or division chiefs that their time will be protected for the duration of the award from other clinical or administrative obligations.

Research support: In addition to the CCTSI KL2 award funds, the scholar's department pledges $25,000/year to support the career growth of the scholar. Scholars typically use these supporting funds to offset personnel costs associated with research conduct such as research coordinators or laboratory technicians. It can also be used for research supplies, reagents, animals, and research equipment as needed. KL2 scholars will be provided office and laboratory space and other infrastructural supports, such as administrative assistance, computer, internet, IRB, and IACUC. Additionally, the CCTSI offsets the cost of performing research by offering free or substantially subsidized biostatistical support for KL2 scholars.

Pilot funding: Diverse opportunities to obtain pilot funding are provided through the CCTSI. For example, pilot funding is available to scholars in the form of a *MicroGrant* that may be used to purchase CTRC services for research protocols conducted at the University of Colorado Hospital, Children's Hospital Colorado, and Perinatal CTRC. These pilot funds provide up to $10,000/year for 3 years to support human subjects' research. Additional

pilot programs funded through other institutional sources are available to scholars, including pilots focused on cross-disciplinary and collaborative team-based research, neuroscience, child and maternal health, community engagement, and novel clinical and translational methods.

Mentoring: Career and research mentoring KL2 faculty will provide time and effort to CCTSI K Scholars in the form of seminars, workshops, mock study sections, review of draft research grant proposals, and attendance at CO-Mentor and LITeS. By ensuring our KL2 scholar's and mentors have free access to CO-Mentor and LITeS, our CCTSI is supporting the growth of a solid mentor-mentee relationship critical to mentee success.

Expanding reach: Institutional funds from Children's Hospital Colorado support 2 Career Awards for Junior Investigators to participate in the KL2 program. Additionally, to attract a more diverse pool of applicants to the KL2 applicant pool, the CCTSI provides matched scholarship with the home department to expand participation of URMs and less resourced disciplines, such as nursing and public health, in the Clinical Faculty Scholars Program, as this is an excellent preparatory program for competitive KL2 applications.

C. RECRUITMENT AND RETENTION PLAN TO ENHANCE DIVERSITY

Of the 21 former KL2 scholars, 62% are women. The percentage of women in the Colorado KL2 program is higher than the national average of women receiving K08 (30%), K01 (47%), or K23 awards (53%)[40]. Racial and ethnic representation of the Colorado KL2 is 29% Asian, 61% white, 5% Hispanic, and 5% American Indian. National trends for underrepresented minority (URM) groups for K awardees are Native Americans 0.3%, Hispanic 3.4%, Asian 14.8%, Black 2.6%, whites 68.1%, and other/unknown/unreported 10.8%. Additionally, 5% of awardees indicated having disadvantaged backgrounds. We have good representation across our affiliates: 20% National Jewish Health, 5% Denver Health, 10% Children's Hospital Colorado and 65% from CU-D. These data demonstrate that our efforts to enhance diversity achieve acceptable success but we are committed to further increasing our KL2 trainee diversity by instituting the following initiatives.

Cara Wilson, a KL2 Director, is also the Vice Chair for Faculty Development in the Department of Medicine. As such, she is uniquely poised to support the recognition and development of URM faculty who may benefit from the KL2 program's support. Importantly, these faculty may include both potential scholars as well as mentors. Sonia Flores, PhD, is Vice Chair for Diversity and Justice in the Department of Medicine. She interfaces regularly with Dr. Wilson and has a long-standing interest in URM research career development. Dr. Flores will serve as an additional resource to ensure diversity of our KL2 program. We will also work with our CU-D American Indian and Alaska Native Programs to solicit KL2 applications from their program's junior investigators through regular engagement with Spero M. Manson, PhD, a Distinguished Professor of Public Health and Psychiatry, who directs the Centers for American Indian and Alaska Native Health, and serves as Associate Dean of Research in the Colorado School of Public Health. A focus of monthly Leadership Council meetings attended by Drs. Wilson, Burnham, Cicutto and Manson will be to identify potential KL2 mentees who are URMs that may be approached by KL2 leadership to ensure their knowledge and interest in the program and to provide them with coaching and resources to compete successfully for this award. Additionally, by providing CCTSI financial support (to cover tuition) for URM investigators to participate in the CFSP, we anticipate increasing the number of URM KL2 scholars.

The CCTSI will be working with CU-D Office of Inclusion & Outreach (OIO) to achieve its priority focus for extending and expanding efforts to increase the number of URM trainees, developing the quality of URM students, and diversifying the disciplinary backgrounds for those committed to CTR careers. To support the recruitment and persistence of URM scholars to the KL2 program, CCTSI will continue our partnership with OIO, whose mission is to "instill diversity into the institutional consciousness; reinforcing equity and inclusion through policies, practices and programs that prepare all faculty, students and staff for a multicultural world." To strengthen recruitment of URMs and broaden the diversity of faculty, trainees and students, the OIO developed a comprehensive plan to enhance diversity. The plan seeks to: (1) Promote the academic advancement and success of URMs, (2) Enhance cultural and diversity instruction throughout the curriculum, (3) Encourage an institutional climate of inclusiveness, respect and understanding, and (4) Promote innovative research and scholarship related to cultural and racial disparities in health and health care. Since implementation in 2007, a sustained doubling of URM enrollment has occurred in the SOM Residency and Fellowship Programs from 3% in 2002-03 to 6% over the past 5 years. Half of these students received scholarship money from a fund created by the CU President, which also provides funds for those with disabilities or disadvantaged backgrounds.

SUMMARY

In summary, our CCTSI KL2 Institutional Career Development program has a strong track in producing outstanding and successful clinical and translational scientists. ***All (100%) of our CCTSI KL2 scholars remain engaged in clinical and translational research***. Sweeney et al.[28] report that 39% of KL2 scholars receive funding within 2 years of program completion compared to our **67% of KL2 alumni scholars receiving NIH research funding within 2 years of KL2 completion**, suggesting that **we are among the top performing KL2 training programs.** Based on new developments and recommendations for best practices in preparing junior investigators for successful and persistent CTR careers and needs assessments conducted by our Evaluation core, we recognize the need for continuous improvements and augmentation. First our KL2 program will now be informed by a conceptual model for achieving academic persistence (See **Figure 1**) based on our CCTSI colleagues[6-7] that articulate 5 guiding best-practice elements for persistence in CTR. Second, acknowledging published recommendations for best practices in training CTR investigators and learning gaps identified via needs assessments completed within our CCTSI community (scholars, mentors), we have identified **four areas of emphasis** for skills development: (1) Interdisciplinary team science; (2) Entrepreneurship; (3) Big data; and (4) Dissemination and implementation extending into community. These areas of emphasis will build on our existing infrastructure and align nicely with the overall CCTSI strategic plan and complement the educational competencies identified by the NIH and the work of the National Workforce Development Domain Task Force. These proposed new efforts will build on the success of our CCTSI KL2 program to provide a comprehensive Institutional Career Development KL2 program for 5 KL2 junior investigator scholar slots for 3 years each at 75% effort, that will foster *outstanding* and *efficient* CTR research education, promote clinical-translational science *competence* and *excellence*, and augment the *impact* of research performed by KL2 scholars. **Our previous CCTSI KL2 scholars have an enhanced and accelerated rate of success for the K to R grant transition, the conduct of research that is impactful to their fields, and are emerging academic leaders and we expect that our enhanced program will lead to even better outcomes and address the national need for highly qualified and successful CTR investigators.**

COMPONENT I: INSTITUTIONAL CAREER DEVELOPMENT CORE (KL2 PROGRAM)

PLAN FOR INSTRUCTION IN THE RESPONSIBLE CONDUCT OF RESEARCH

Training in the ethical and regulatory principles, including Responsible Conduct of Research (RCR) and Good Clinical Practice (GCP), is critical to the efficient conduct of clinical-translational research (CTR) and maintaining societal trust in the research enterprise and thus is an essential part of the education and training KL2 Career Development Training Program at the Colorado Clinical and Translational Sciences Institute (CCTSI). The University of Colorado Denver (CU-D) and the CCTSI believe that RCR training is an essential educational component for KL2 Scholars pursuing CTR careers. Because RCR is most effective in the scope of daily activities, the plan for RCR training will be tailored to meet the specific needs of the individual scholar. However, all CCTSI KL2 trainees will complete a responsible conduct of research and ethics course that includes Good Clinical Practice, which will be an identified milestone and review criterion of their ICDP. The CCTSI and the University will provide several RCR educational opportunities to KL2 Scholars, their mentors and collaborating faculty and staff. Educational opportunities are designed to be in full compliance with the policy requirements for RCR education promulgated by NIH in NOT-OD-10-019.

A. Format

The CCTSI infrastructure provides multiple modalities and initiatives to ensure that all KL2 Scholars are prepared to conduct efficient, safe, best practice oriented translational research. Modalities of instruction will include: 1) formal graduate level courses (CU-D: CLSC 7150, CLSC 7151, CLSC 6590, BIOS/PHCL 7605, IDPT 8890) involving lectures, face-to-face discussion, and application of content that follow NIH recommended curricular requirements (NOT-OD-10-019), 2) lunch hour workshops offered through the Regulatory Knowledge and Support (RKS) Core, 3) short courses offered through the RKS Core, 4) ethics conferences and guest lectures, and 5) online modules for self-paced instruction. **All KL2 Scholars will complete a formal research ethics and responsible conduct course that entails over 15 hours of face-to-face instruction, dialogue, application PLUS completion of CITI modules (HIPAA, GCP, human subject protection, and RCR).**

***A.1.Basic training*.** All KL2 Scholars will be required to complete Collaborative Institutional Training Initiative (CITI) online modules for Basic Course in the Protection of Human Research Subjects, the CITI HIPAA Course, CITI Responsible Conduct of Research and the CITI Good Clinical Practice module and, if appropriate, completed the required CITI refresher courses on an every three-year basis. Scholars that have not already completed CITI modules and an approved ethics and RCR course before starting the KL2 program, will complete the CITI modules AND a 4 hour face-to-face *Getting Started in Research Workshop* offered by CCTSI's Regulatory and Knowledge Service Core on the last Wednesday of July before they receive KL2 funding.

A.2. Advanced Training. All KL2 Scholars will be required to complete an Ethics and Responsible Conduct of Research course that follows NIH recommended curricular requirements (NOT-OD-10-019). KL2 Scholars will complete the Clinical Science (CLSC) Ethics and Responsible Conduct of Research course at some point during their 3 years of KL2 funding and support. It is anticipated that some of the Scholars will have already completed a comparable graduate course within 20 months of starting the KL2 program and they will not be required to repeat the course during the first year of the KL2 unless the course does not meet the NIH recommended curricular requirements (NOT-OD-10-019). Many of the KL2 Scholars performing trials complete the CLSC course, *Conducting Clinical Trials for Investigators*. Topics covered in this course will include GCP, common deficits in clinical trials, grant management, data management, preparing for audits, and regulations surrounding studies evaluating devices and therapeutics (drugs). Both courses include the application of learning through assignments relevant to the Scholar's current research endeavors. An assignment example is to identify the process of setting up a mock clinical trial including identifying budget items, thinking about staff needed, writing a subject management protocol, planning recruitment strategies and characterizing informed consent process. In addition, RCR, GCP, and associated topics will be integrated into the monthly KL2 Scholar Seminars. Scholars will also be strongly encouraged to attend other educational opportunities offered through the Regulatory and Knowledge Core, such as lunch hour workshops, short-courses, ethics conferences, or individual consults.

B. Subject Matter

Topics covered in required coursework and educational opportunities will include: ethics and regulation of human subject protection, preparation of a consent form, human embryonic stem cell research, industry-sponsored research, confidentiality, respect, identifying legal and regulatory constraints, scientific integrity, ethical theories and principles, live vertebrate animal subjects in research, federal and institutional guidelines for research pertaining to human and animal models, safe laboratory practices, data acquisition, management, ownership and sharing, mentor/mentee responsibilities and relationships, collaborative research including collaborations with industry, conflicts of interest, peer review, and responsible authorship and publication. Online CITI training in Responsible Conduct of Research offers modules by discipline type: biomedical, social and behavioral sciences, physical sciences and humanities.

C. Faculty Participation

Research mentors will be required to demonstrate completion of training for RCR and GCP within the last 3 years. A requirement of all personnel involved in any clinical-translational research throughout our institutions is the completion of CITI online training modules for HIPAA, GCP, human subject protection, and RCR in addition to attending face-to-face workshops of no less than 8 hours occurring no less than every 3 years. All University of Colorado Denver faculty/staff are able to take any of these courses at no cost through their University tuition reimbursement program.

KL2 Program faculty/mentors will meet at least weekly with KL2 Scholars and oversee progress according to the scholar's Individual Career Development Plan (ICDP) for research, training, and career development, including completion of ethics, GCP and RCR training. Research mentors will be responsible for ensuring that the scholar adheres to ethical and regulatory practices (including RCR and GCP training, IRB and IACUC approvals, when appropriate), maintains research-training certificates and documents such on the ICDP. KL2 Program faculty will be involved in both formal and informal instruction related to RCR and GCP. Information exchange will occurs in the course of daily research interactions, clinical experiences, and other research related situations and more formally as discussion leaders, speakers, and lecturers. Dr. Burnham, KL2 Co-Director, provides 3 workshops during the KL2 monthly Seminars on topics related to RCR, GCP, regulatory requirements and ethical principles in the conduct of CTR.

In addition to KL2 faculty/mentors, Dr. Marilyn Coors, (Regulatory Core), Dr. Allan Prochazka (CLSC program) and Dr. Barbara Hammack (Regulatory Core and CLSC) are instrumental in educational opportunities and courses. **Allan Prochazka MD, MSc** is the past chair of CU-D's IRB and has performed research on informed consent, including a randomized trial of repeat back to enhance surgical informed consent. Since 1999 he has taught responsible conduct of research and research ethics graduate classes for the Clinical Science Program. **Barbara Hammack PhD** is the Manger of Research Services for the CCTSI and the University and has expertise in protocol development. She will be a tremendous asset for KL2 junior investigators in developing necessary skills for success in CTR. She teaches the CLSC course, *Conducting Clinical Trials for Investigators* and will be one of the KL2 Seminar speakers. **Marilyn E. Coors PhD** is Associate Professor of Bioethics at the Center for Bioethics and Humanities and Director of Research Ethics for the CCTSI. She holds a Ph.D. in bioethics, and the ethical issues in clinical genetics and genetic research are the foci of her research, teaching and professional service. She will provide cross-disciplinary ethics education through the KL2 Scholars seminars and ethics conferences held throughout the year and provide individual research ethics consultations.

D. Duration of Instruction

All KL2 Scholars will complete a formal research ethics and responsible conduct course that entails over 15 hours of face-to-face instruction, dialogue, application PLUS completion of CITI modules (HIPAA, GCP, human subject protection, and RCR). Courses are offered every year during spring and fall terms and have been specifically designed and designated by the University of Colorado Denver to meet all NIH guidelines requirements. In addition, another 10 hours of discussion and instruction will occur through the KL2 Scholar Seminars. Several KL2 Scholars will also be complete a 23-hour contact hour course, *Conducting Clinical Trials for Investigators,* as part of their ICDP. See the Format section above for additional detail.

E. Frequency of Instruction

Frequency and type of instruction depends on the individual scholar but all scholars will complete RCR, GCP and ethics training. As most scholars will start the CCTSI TL1 Training Program in July, in the middle of a summer term, scholars who have not completed an approved ethics and RCR course and the required CITI online modules (HIPAA, GCP, human subject protection, and RCR) will be required to register and attend the 4-hour, face-to-face Getting Started in Research Workshop offered by CCTSI's Regulatory and Knowledge Service Core provided in July. Scholars that have not completed an approved course will subsequently be required to demonstrate fall term enrollment in the CLSC's ethical and responsible conduct of research course and, then in January, submit proof of course completion with a minimum grade of a "B" otherwise KL2 funding disbursement will not occur. Scholars who have fulfilled the RCR course and CIT module required within 20 months of starting the KL2 program will be allowed to repeat the RCR and ethics course and CITI online modules in year 2 of their training. Additionally, at least 15 hours of content and discussion will occur over the monthly KL2 Scholar Seminars.

F. Compliance

KL2 funding will not be provided to Scholars until proof of completion or enrollment is provided to the KL2 Program Director and Program Administrator. Research mentors will also be required to demonstrate completion of training for RCR and GCP within the last 3 years. In addition to the documentation required by scholars and their mentors, the Colorado Multiple Institutional Review Board requires proof that all trainees and personnel involved in research have successfully completed the CITI Basic Course in the Protection of Human Research Subjects, the CITI HIPAA Course, CITI Responsible Conduct of Research, and the CITI Good Clinical Practice module and have required completed CITI refresher courses on an every three year basis.

As detailed in Component E. Research Methods (RKS section) and Component G. Network Capacity, CU-D in collaboration with UCHealth and Children's Hospital Colorado, will transition the current pre-review and management of study protocols into OnCore (a CTMS) to further streamline processes. We will use the centralized database provided by OnCore to track mandatory training listed above, licensing of and credentialing of research personnel. Members of the research team will only be granted access to OnCore upon completion of the requisite GCP and RCR training. Through these courses and Oncore, standard operating procedures, template forms and checklists will be made available for research teams that can be adapted to meet their needs. Site initiation visits and periodic audits by the Regulatory Core will trainees and their mentors in meeting regulatory standards when operationalizing their protocols.

G. Review and Quality Improvement

Every year the Translational Workforce Development, KL2 Career Development, and Regulatory Cores will review participant evaluations and discuss strengths and limitations of current offerings to identify the need for and types of revisions necessary. For the last 8 years the CLSC Ethics and Responsible Conduct of Research Course receives very high marks (scores over 4.5 on a 5 point scale) in terms of relevance, stimulation of critical thinking, application, and knowledge of the professor/instructor. Every year Dr. Prochazka, the course professor, is nominated for Best Teacher of the Year Award within the CLSC. The CCTSI is strongly committed to upholding the highest ethical, regulatory and professional standards in research endeavors and ensures that anyone involved in clinical and translational research are trained and remain current in best practices.

COMPONENT I: INSTITUTIONAL CAREER DEVELOPMENT CORE (KL2 PROGRAM)

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COMPONENT J: NRSA TRAINING CORE (TL1 PROGRAM)

PROJECT SUMMARY/ABSTRACT

Highly qualified and thoroughly prepared interdisciplinary teams fuel discovery. The **overarching goal** of the proposed **TL1 Training Program** is to build a diverse workforce of clinical and translational researchers (CTR) by enhancing our capacity for team-based research training spanning the pre-clinical to population health spectrum, and by leveraging our minority student pipeline. Our TL1 training program, **Team Oriented Training across the Translational Sciences Spectrum (TOTTS),** *requests funds for 15 slots focused on recruiting diverse translational researchers, of which 25-30% will be underrepresented minority (URM) trainees.* TOTTS will target three groups of future CTR investigators: a) biomedical PhD students, b) health professional trainees completing their doctorate (pre-doctoral) or post-doctoral medical residents, and c) veterinary post-doctoral trainees. To achieve these goals the following **Specific Aims** are proposed: **Aim 1**: Provide rigorous training that builds core competencies in clinical and translational research to become successful translational researchers. **Aim 2**: Mentor trainees using individualized career coaching and a multi-disciplinary team approach to provide experiences and perspectives in the conduct of translational research across the study lifespan and translational spectrum. **Aim 3:** Support the future success of trainees through integration into the clinical-translational science community, and disseminating scholarly products while building a scholarly portfolio. The overarching theme of Diversity in Accelerating Research Excellence (DARE) will be integrated into TOTTS activities. Specific aims will be achieved through using individualized career development plans, mentorship, coursework and career development programs, immersion into CTR, and translation of CTR. Career development initiatives will be offered in team science, leadership, and translation through community engagement, dissemination and implementation. All trainees will complete training in the Responsible Conduct of Research and Good Clinical Practice. Individualized career development plans will facilitate oversight and guidance by the mentoring team for each trainee in completing milestones and goals. Each trainee will have a TOTTS Program Director mentor, a research mentor, and a translational mentor, who will be a clinical mentor for non-clinicians and veterinary trainees and either a biomedical researcher or community researcher for clinician trainees. URM trainees will also have a URM mentor and 4 interactive seminars to support success. Mentors and mentees will complete the CO-Mentor program to solidify effective mentoring relationships. Immersion into CTR will involve meaningful, project-oriented CTR research experiences. Program diversity will increase through partnering activities with the School of Medicine's Office of Diversity and Inclusion and the University's Office of Inclusion and Outreach. Key outcomes for the program will be persistence in CTR, number of peer-reviewed publications and submitted and awarded grants, and URM diversity of trainees.

COMPONENT J: NRSA TRAINING CORE (TL1 PROGRAM)

PROGRAM PLAN

SPECIFIC AIMS

"We can't solve problems by using the same kind of thinking we used when we created them."[1] Albert Einstein's aphorism captures the dilemma central to the clinical and translational research (CTR) agenda to accelerate research and improve its translation for societal improvement. Highly qualified and thoroughly prepared interdisciplinary teams fuel discovery. The **overarching goal** of our **TL1 Training Program** is to ultimately build a diverse workforce of clinical and translational researchers by enhancing our capacity for team-based research training spanning the pre-clinical to population health spectrum, and by leveraging our minority student pipeline. We are proposing a TL1 training program, **Team Oriented Training across the Translational Sciences Spectrum (TOTTS),** *for 15 TL1 slots focused on recruiting diverse translational researchers, 25-30% of which will be for trainees from underrepresented minority (URM) backgrounds.* TOTTS will target three groups of future CTR investigators: a) biomedical PhD students, b) health professional trainees completing their professional doctorate (pre-doctoral) or post-doctoral medical residents, and c) veterinary post-doctoral trainees. To achieve these goals we propose the following **Specific Aims**:

Aim 1: Provide rigorous training that builds core competencies in clinical and translational research to become successful translational researchers.

Aim 2: Mentor trainees using individualized career coaching and a multi-disciplinary team approach to provide experiences and perspectives in the conduct of translational research across the study lifespan and translational spectrum.

Aim 3: Support the future success of trainees through integration into the clinical and translational science community, and disseminating scholarly products while building a scholarly portfolio.

Our motto, Diversity in Accelerating Research Excellence in CTR will be integrated into our programs and activities. Over the next 5 years, we propose TL1 training efforts to span the translational spectrum, from predictive pre-clinical animal models, to human clinical trials and community research, leveraging the full spectrum of research affiliations encompassed by the CCTSI. In a novel approach to expanding the T0.5 - T1 end of the translational spectrum, we propose engaging the Colorado State University's (CSU) world-renowned veterinary medicine program, a program with significant strengths in both basic and clinical/translational sciences, to provide an ideal platform for veterinarians and human clinical scientists to synergize expertise to further the discovery and its application to shared disease models for the advancement of diagnostics and treatment. We use the term "T0.5" to acknowledge that natural animal model research can translate into clinical advances both for humans and for animals, and address the need for workforce development articulated in the NIH Physician Scientist Workforce report[1] and others[2-4]. We additionally focus on recruitment of under represented early career scientists to expand diversity of the workforce—a high priority of the NIH[5].

Our TL1 program will be informed by the work of our CCTSI colleagues, Nearing and Manson, who make 5 recommendations, based on the literature and our CCTSI experience recruiting, developing and retaining CTR investigators. Their model for trainee persistence in CTR includes: 1) Create a **seamless pipe-line** for forming strategic partnerships to achieve continuity of support for trainees; 2) Provide **meaningful research** opportunities to support identity formation as a CTR investigator and sustain motivation and persistence in CTR; 3) Foster **effective mentorship** and **peer support** to support integration into the CTR culture; 4) Advocate for supportive environments to **diminish** "**pull**" factors drawing people away from CTR careers; and 5) Support program evaluation - especially **longitudinal outcomes** - to guide and revise training efforts. By creating a climate for diversity and team oriented science with quality, evidence-based programs and integrated networks of support, we will create the training program and environment necessary for diverse trainees to progress successfully and efficiently through the pipeline to achieve NIH's vision of a robust CTR workforce that is ready and capable to face challenges for achieving health equity.

Common Abbreviations used in this Component

CTR	Clinical and Translational Research	CVMBS	College of Veterinary Medicine and Biomedical Sciences at CSU
CLSC	Clinical Science Graduate Program	ICDP	Individual Career Development Plan
CCTSI	Colorado Clinical and Translational Sciences Institute	LITeS jr	Leadership in Innovative Team Science Program for Junior Investigators
CO-Mentor	Colorado Mentoring Program	MAC	Mentoring Advisory Committee
CCTSI	Colorado Clinical and Translational Sciences Institute	SciTS	Science of Team Science
CSU	Colorado State University	TOTTS	Team Oriented Training across the Translational Sciences

TL1 TRAINING PROGRAM

A. BACKGROUND

A.1 Rationale

TL1 Vital Statistics	
Persistence	86% persistent in clinical and translational research
Publications	5 publications per trainee for a total of 222
Diversity	64% of trainees and alumni are women

The mission of the CTSA national program is to infuse biomedical research with new perspectives, methodologies, and technologies. Central to achieving this mission is creating a robust translational research workforce prepared to rigorously and efficiently conducts interdisciplinary team oriented clinical and translational research (CTR). To prepare this workforce, it is imperative to offer CTR TL1 programs to expose and retain trainees early in their career. In this proposal we request support for 9 pre-doctoral and 6 post-doctoral TL1 training positions to develop future CTR team-oriented scientists. The Colorado Clinical and Translational Sciences Institute (CCTSI) is the ideal setting for this diverse multidisciplinary TL1 Training Program, as the CCTSI's affiliated universities include schools/ programs spanning the health sciences (Medicine, Nursing, Pharmacy, Public Health, Rehabilitation, Psychology), bioengineering, regulatory sciences, social sciences, biomedicine, veterinary medicine and other disciplines. Trainees of these schools/programs will be targeted for participation in the CCTSI TL1 program (See **Table 10** for enrollment). Emphasizing the importance of team-oriented translational science our TL1 program will be called **Team Oriented Training across the Translational Sciences (TOTTS).** The rationale for transforming our current successful TL1 program to the newly formatted TOTTS program is based on the following 3 new priorities: 1) expand the spectrum of trainees to include veterinary medicine fellowship trainees and clinicians; 2) embrace Diversity to Accelerate Research Excellence (DARE) through activities of recruitment, mentorship and retention of underrepresented minority (URM) scientists as TOTTS trainees, with an emphasis on programming to overcome common challenges and barriers experienced by URMs; and 3) optimize programmatic elements to develop skills for team-oriented CTR across the full translational spectrum.

The inclusion of **veterinary scientists** in our TL1 program is in response to national data showing insufficient numbers of veterinarians are trained in translational biomedical research—despite the significant need for their expertise in comparative translational medicine to accelerate bench to bedside discoveries.[1] The capacity of veterinarians to fill this national need is severely limited due to insufficient opportunities for postdoctoral training in research as highlighted in several reports including the 2015 NIH Physician Scientist Workforce report, National Academy of Sciences analyses and the NIH ORIP One Health Workshop: Integrating the Veterinarian Scientist into the Biomedical Research Enterprise.[1-4] These documents also stressed the need for veterinarians to enhance translational research by consideration of the intersection of human, animal and environmental health (so-called One Health)**. Thus, our TOTTS program will address this call-to-action by preparing veterinary clinical scientists from Colorado State University, a CCTSI partner institution, and integrating them into multi-disciplinary team-oriented CTR across the translational spectrum**.

Recognizing the enhanced success of diverse teams of researchers, CTSAs are charged with diversifying their trainee populations. The NIH is committed to increasing the number URMs pursuing careers in clinical and translational research for several reasons. First, racial and ethnic disparities exist along the biomedical workforce career pipeline.[5-6] Additionally, we observe that racial and ethnic minority patient populations suffer disproportionately from diseases that can be prevented or controlled.[7-9] URM investigators are more likely than their majority counterparts to focus on conditions and risk factors that most threaten these populations.[5-7,9] Equally important, they bring unique "insider" perspectives and experiences that enhance their capacity to understand factors underlying health disparities.[5-7,9] Diverse teams are smarter than homogenous ones.[10-14] Working with people who are different challenges your brain and makes you think in new ways. Diverse teams of scientists produce higher impact research findings that yield better outcomes than less diverse teams.[11-14] **Therefore, the CCTSI has made diversity a priority focus in accelerating excellence in our training programs.** TOTTS supports this priority by expanding efforts to increase the number of URM trainees and developing activities focused on meeting the preparedness and readiness needs of URM trainees to overcome challenges and obstacles more commonly encountered by URMs. Several of our critical goals over the next funding period will be to diversify and retain our CTR workforce, improve persistence of URMS in CTR, and conduct meaningful research to address racial health inequalities.

A.2. Need for CCTSI TL1 TOTTS

The 29 existing T32 level training grants at CU-D provide vibrant training opportunities that focus on training a future biomedical workforce in multiple but very focused areas, many of which emphasize basic research.

Although at first glance this may appear to meet the needs at our institution, there are at least 6 reasons that justify this proposal for the unique attributes of a new expanded CCTSI TL1 TOTTS program. (1) There is high unmet demand for these TL1 CTR trainee slots beyond our current capacity. Based on our previous application cycles, 20-28 meritorious applications are submitted each year for our previous 8 slots. (2) For future career success as a member and leader of an interdisciplinary CTR team, a comprehensive program is necessary that prepares trainees for and in models of team oriented CTR. (3) Our TOTTS program is uniquely modeled for achieving academic and CTR persistence with tailored supports for URMs. (4) Our program will be a catalyst and role model for other pre- and post-doctoral training programs on campus to offer their trainees opportunities to build leadership and team skills. Other programs are now considering offering their trainees workshops to build leadership and team skills, as we have built into this proposal. (5) Our CCTSI External Advisory Committee has consistently advised us over the years to extend our TL1 program to physician and clinician trainees to expand the pipeline for clinician scientists. When we initially applied for our CTSA TL1 program the request for applications specifically requested PhD trainees. Given our ability to expand the TL1 program and be responsive to the current FOA, we will be attracting, recruiting and supporting medical students and residents as well as other doctoral health professional students. (6) Previous experience with the TL1 program and the literature highlight the need for engagement of trainees from URM backgrounds to accelerate CTR. Our close partnership with the University of Colorado's Office of Inclusion and Outreach and the School of Medicine's (SOM) Office of Diversity and Inclusion will strengthen the ability of the TOTTS program to recruit, train and retain trainees with diverse backgrounds.

A.3. Model for Persistence of a Diverse Clinical and Translational Research Workforce

Individual, social, historical, and contemporary issues contribute to the challenges confronted by trainees interested in careers in CTR. These challenges are dramatically amplified for minorities and include race and ethnicity-based recruitment disparities, differences in prior educational opportunities, and disparities in exposure to training programs.[15] Our TOTTS programmatic activities will be reflective of our CCTSI colleagues', Nearing and Manson[16-18], conceptual model for educational success and CTR persistence. The major tenet of the conceptual model is that trainee integration into the academic and social realms of the university strengthens commitment to the institution and the likelihood of persistence in CTR. The conceptual model for CTR persistence is presented in Figure 1 and offers a synopsis of theories and empirical research regarding factors most predictive of scholarly engagement, achievement and persistence, with a specific emphasis placed on the experiences, supports and outcomes for underrepresented minorities in CTR.[19-28] The conceptual model features "goals thinking" and "pathways thinking" as central to the formation of a conceptual roadmap for career success. The importance of goals, pathways and agency thinking are drawn from Hope Theory, developed by Snyder,[24-28] postulates that hope is principally a cognitive process that involves establishing goals (*goals thinking*), determining strategies or paths to achieve a given goal (*pathways thinking*) and maintaining the mental and emotional (i.e., motivational) energy necessary for goal pursuit (*agency thinking*). Research suggests that these cognitive processes are amenable to intervention – that even for those from disadvantaged backgrounds, who may have been affected by negative messages received during early stages of their academic careers and self-doubt due to the dearth of available role models, opportunities may be intentionally scaffolded to experience the accomplishment of incrementally more challenging goals and the concomitant sense of agency that can be achieved as part of the personal/professional growth process.[28]

Based on our Model of Persistence for a Diverse Clinical and Translational Research Workforce (**Figure 1**), **five overarching strategies** will be applied in addressing the challenge of educational and CTR persistence.[18]

(1) Create a **seamless pipeline** by forming strategic partnerships to achieve continuity of support for trainees and collective impact. We will leverage the assets and efforts of the university to establish a seamless pipeline that facilitates CTR career counseling that begins in middle and high schools (CU-D URM pre-pipeline program; See below Section C) and extends to staff and faculty. Specifically, CU's Office of Inclusion and Outreach and the SOM's Office of Diversity and Inclusion URM pipeline of programs will be leveraged to attract and recruit highly prepared applicants and trainees from diverse backgrounds. Additionally, to facilitate the creation of a "seamless" pipeline to ensure that trainees receive continuity of support throughout their stages of career development and that programs are responsive to learners' needs, CCTSI and university educational, training and career development program directors and leaders will form a **Leadership Advisory Council** that will meet monthly to intentionally work and organize efforts in a coordinated and integrated fashion.

(2) Provide **meaningful research opportunities** to support identity formation as a scientist and sustain motivation to pursue and persist in CTR careers. Engaging budding CTR investigators in meaningful research opportunities fuels motivation and will be accomplished by a) having trainees reflect on how their research

interests and career support their personal values and goals; b) having mentors assist mentees to clarify goals and motivations; c) supporting trainees participation in meaningful research; and d) facilitating collaborations across the translational spectrum. Every TOTTS trainee will have a mentored research project meaningful to him/her providing essential engagement for learning, developing competence, socialization, and identification and integration into the CTR workforce. Additionally, research projects will lead to trainee presentations and publications, which builds a stronger portfolio and increases their competitiveness in the future.

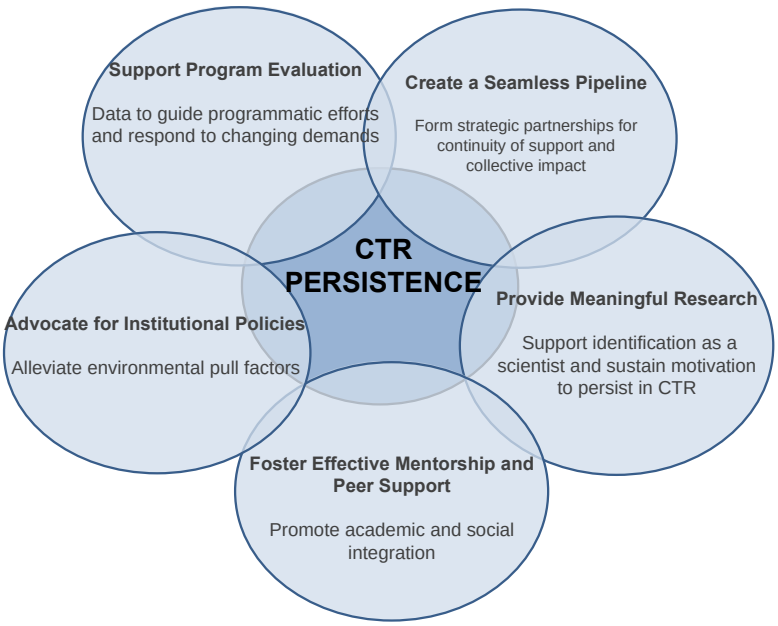
(3) Foster an environment for **effective mentorship and peer support** to promote academic and social integration. Our program will provide mentorship and peer support, two of the most effective strategies for promoting social and academic integration[18]. TOTTS mentors will assist with: a) setting strategic goals, b) devising pathways to success that include alternative strategies when challenges emerge, c) accessing resources and services, d) developing CTR competencies, and e) providing emotional support. TOTTS twice-monthly seminars will create affinity group(s) and provide peer support and mentorship as strategies to increase satisfaction, decrease the feeling of marginalization, and increase sense of inclusion, all of which promote integration into the CTR workforce. Additionally each trainee will have mentors for the contexts of research, translation, and career development-scholarship that will form a Mentor Advisory Committee. To address the need for effective mentoring relationships, trainee mentee-mentor dyads will attend the CCTSI's CO-Mentor program, a formalized program for effective mentoring relationships. Additionally, URM TOTTS trainees will have a URM mentor for contextualized support and guidance for succeeding in CTR.

(4) Advocate for institutional policies **alleviating environmental pull factors**. Environmental pull factors are competing or conflicting demands with trainee engagement, integration, and performance that ultimately diminish persistence. The Leadership Advisory Council will proactively advocate for institutional policies to support the CTR workforce in their work. For example, to support creating a culture that values diversity and recognizes that excellence requires diversity, career development activities will be provided that addresses cultural humility, holistic review of applications/dossiers, unconscious bias, and mentorship for diverse mentees. These topics will be integrated into the following professional development activities that serve TOTTS trainees and faculty, as well as the broader CCTSI workforce: TOTTS seminars, workshop for TOTTS Recruitment and Selection Committee, CO-Mentor, and LITeS (Leadership for Innovative Team Science).

(5) Support program evaluation - particularly, the **examination of longitudinal outcomes** - to guide programmatic efforts and respond to changing demands. The CCTSI Evaluation Core will serve on the Leadership Advisory Council and present semi-annually on metrics for TOTTS.

These 5 overarching strategies identified by Nearing et al.[18] were informed by our experience leading and evaluating programs across the educational and career development pipeline and extensively reviewing the literature across multiple disciplines. Our TOTTS program applies lessons learned and best practices to prepare a highly qualified workforce of CTR investigators. (Described in **Section B.5**)

Figure 1. Conceptual Model: Achieving Persistence in a Diverse Clinical and Translational Research Workforce



A.4. Infrastructure to Support TL1 Program

A.4.1. Supporting Institutions. The CCTSI has a large basic biomedical and clinical research infrastructure, with the ability to address all possible research questions. Our strong CTR training programs encompass the spectrum of professional health and life sciences careers. The CCTSI partnership includes CU-Denver (CU-D), CU Boulder (CU-B), Colorado State University (CSU), 6 hospitals and >20 community organizations.

CU-D is a comprehensive university within the region's largest metropolitan area, including the Downtown Denver Campus and the Anschutz Medical Center (AMC) Campus. With more than 27,000 students and 100 degree programs in 12 schools and colleges, CU-D awards more than

3,400 degrees each year and more graduate degrees than any other institution in Colorado. The **Downtown Denver Campus** is the most ethnically diverse college campus in Colorado, providing opportunities for improving minority and underserved population participation in training. **CU-AMC,** a 230 acre health science campus with over $4 billion in investments, is the only Academic Health Education Center within Colorado and the central location of the CCTSI, and is home to 6 health profession schools. Over 60 inter-disciplinary research centers, institutes and biotechnology core facilities form the nexus for outstanding basic, translational and clinical research and training, integrated with many of the programs and core services of the CCTSI. An adjacent biotechnology park helps facilitate close collaboration between University investigators and the private sector. **SOM/Office of Diversity and Inclusion** is striving to build an inclusive culture and not just implement a diversity strategy in danger of becoming a taskforce to count people. Thus their activities are focused on the learning environment, curriculum, community service activities, and the institutional climate. Example activities include the **URM Pipeline of Programs,** which includes 15 summer undergraduate research programs, a rural health scholars program, and the Colorado Collegiate Health Professions Development program. The **Colorado School of Public Health (CSPH)** was created in August 2007 as a partnership between CU-D, CSU and University of Northern Colorado. The CSPH plays a major role in training and career development programs in biostatistics, data sciences, study design and health policy within the CCTSI, and houses the CCTSI Biostatistics (BERD) Program. **CU-D Graduate School** offers 21 PhD and 5 Masters programs. PhD degrees may be obtained in multiple basic and clinical science fields, including the Clinical Science (CLSC) program.

CU-B is a premier academic and research University, including 8 schools and colleges and 44 doctoral degree programs. With 5 Nobel Laureates on faculty, there is a rich history of innovative discovery leading to human applications in fields of biotechnology, medical research, biochemistry, biology, and engineering. Interdisciplinary collaboration between CU-B and CU-D investigators has led to major discoveries in bioengineering, tissue engineering, congestive heart failure, congenital heart disease, the microbiome, pharmaceutical biotechnology, and molecular biology.

CSU joined the CCTSI alliance in 2013. It is a public land-grant institution founded in 1870 and located in Fort Collins, a midsize city one hour north of Denver. CSU includes 8 colleges, including the renowned College of Veterinary Medicine and Biomedical Sciences. CSU also has leading research programs in animal science, team science, occupational therapy and occupational health, health and exercise science, atmospheric science, clean energy technologies, neuroscience, health physics, and environmental science. In the next grant cycle, the **CSU College of Veterinary Medicine and Biomedical Sciences (CVMBS)** will participate in the CCTSI TOTTS program through our novel integrated CTR training program for post-DVM/VMDs. ***CSU's CVMBS is ranked third in the nation by U.S. News and World Report*** *and has* over 540 students, 250 faculty, 5 Programs of Research and Scholarly Excellence, 19 post-DVM residency training programs, 6 Distinguished Professors, an extramural research budget of ~$50M (fiscal year 2016), and a 60+year record of post-DVM graduate training. With NIH recognition of the importance of natural animal models for human disease (what we have labeled T0.5 translation) and of One Health, CVMBS is poised to contribute outstanding candidates for the translational CTR training pipeline. CVMBS has significant experience in evaluating, selecting, and recruiting high quality post-DVM candidates for training in research-focused graduate programs. CVMBS faculty participate in several established research affinity groups at CSU that have direct human application, including the Arthropod Borne Infectious Disease Laboratories, the Mycobacteria Research Laboratories, the Retroviral Research Laboratories, the Animal Reproduction Biotechnology Laboratory, the Flint Animal Cancer Center, Orthopedic Research Center, Center for Regenerative Medicine, the Prion Research Center, the Translational Medicine Institute, and the Center for Molecular, Cellular & Integrative Neurosciences. Fifty-eight CVMBS faculty with experience in mentorship of veterinary research trainees are listed as participating mentors in this proposal. (**see TL1 tables**).

In addition to graduate training, CSU CVMBS offers specialty residency training in a variety of clinical specialties, including orthopedic/soft-tissue surgery, internal medicine, oncology, neurology, dermatology, ophthalmology, emergency/critical care, diagnostic imaging, clinical and anatomic pathology, and comparative/ laboratory animal medicine similar to their human analogs in scope, length and rigor. The Flint Animal Cancer Center has an established and vigorous clinical trials program to evaluate novel therapies that may inform clinical development of novel human cancer therapeutics. CCTSI support of a Natural Animal Models Core during the current funding period resulted in increased interactions and synergies in translational studies between CU-D and CSU researchers in areas of stem cell research, interventional cardiology, and cancer therapies, and has enhanced veterinary clinical trials capacity at CSU.

Collaborative research and education programs have occurred for decades among CSU, CU-D and CU-B faculty (e.g., over 80 ongoing CSU-CU-D collaborations and over 300 CSU CCTSI members). CSU is a partner in the

CU-D Comprehensive Cancer Center (NCI), the Nutrition and Obesity Research Center (NIDDK), and the CSPH. Other major CU-D research collaborations are in infectious disease, exercise physiology, HIV/AIDS research, and community engaged research. CSU's partnership in the CCTSI has expanded the use of natural animal models of human diseases in translational research projects, bridging across CCTSI institutions.

B.4.2. CCTSI Resources for TOTTS Program. The CCTSI has developed extensive infrastructure and programs that will be leveraged by the TOTTS program to sustain a high-impact translational workforce essential for a successful and vibrant research enterprise. This includes the following specific programs:

1. CCTSI's Biostatistics, Epidemiology, and Research Design (BERD) core will provide TOTTS trainees with opportunities to collaborate and consult with biostatisticians to assist with study design and analysis and participate in innovative training programs for non-statisticians. Study Jump Starts available to trainees will bring together statisticians, database-informational consultants and regulatory consultants at one time to discuss the study in terms of best practices, next steps and anticipatory problem identification and strategizing.

2. Our CCTSI network of 5 **Clinical Translational Research Centers (CTRCs**) provides inpatient and outpatient research facilities and resources, which include dedicated inpatient and outpatient research space and equipment, research nursing, bionutrition, vascular ultrasonography and Core laboratories. **The CCTSI Translational Informatics Program** develops research informatics tools and provides training and support for research database and informatics needs. Resources that will be available to trainees include: (1) **REDCap,** a web-based, HIPAA-compliant study data management solution adopted widely by members of the national CTSA consortium; and (2) **SeDLAC** (Secondary Database Library and Analysis Center) to access large national population-based datasets from NCVS and AHRQ. The team maintains data management needs across the CCTSI, including backups, security, networking, access controls, and desktop support.

3. CCTSI Health Data Compass (Compass) is a multi-institutional data warehouse funded by the UCHealth System, Children's Hospital Colorado, and the CU-SOM, specifically designed to support data discovery and data sciences methodologies that integrate large-scale biological, clinical, administrative, regional, state and national data sets, such as environmental exposures and CDC data.

4. CCTSI's Regulatory Knowledge and Support Core (RKS) will help TL1 trainees navigate regulatory requirements and provides training and consultation in the Responsible Conduct of Research (RCR). Educational offerings (lunch hour workshops and short courses) occur every month throughout the year with topics such as scientific misconduct, conflict of interest, data management, informed consent, research ethics, human and animal protection, laboratory protection, and Good Clinical Practice (GCP). A requirement of all people involved in clinical-translational research at CU-D is the completion of the online CITI HIPAA, GCP and RCR modules in addition to attendance at face-to-face workshops no less than every three years.

5. The **Clinical Science Graduate Program (CLSC)** is the primary CU-D degree-granting and coursework-offering program for advanced training in clinical translational research, and has been incorporated into the CCTSI since 2008. The program's goal is to prepare nationally competitive clinician- and clinical-translational scientists and thus is perfectly aligned with the mission of TOTTS. Evidence of the importance of the CLSC and its lead role for education and training future clinician scientists is the partnerships formed with more than 15 federally funded training (T32 and K12) programs, as well as other training programs. The program is truly interdisciplinary and promotes team science through engaged learner activities that include participation in collaborative real-world assignments, review of one another's work (grants/proposals, data collection tools, etc.), debates, presentations and socialization. The program offers a PhD degree in Clinical Investigation and Health Outcomes, Health Services Research and Health Information Technology, and a Master's in Clinical Science (MSCS). Degree programs and courses are designed to be multi-disciplinary and help trainees achieve proficiency in clinical science and translation and align with the NIH CTR competencies. Coursework includes biostatistics, clinical studies and trial design, critical appraisal of clinical and translational sciences literature, ethics, regulatory principles and responsible conduct of research, operational issues in conducting clinical trials, publishing, and grant writing. Over the past 4 years, the CLSC program graduated 14 PhD and 47 MSCS students. *Currently 78% of CLSC alumni (MSCS=62; PhD=57) hold grant support with 55% and 45% of PhD and MSCS graduates, respectively, holding a federally-funded grant as a PI or Co-PI. In total, our alumni have held over 370 grants in the last four years, over 670 grants since graduation, and published over 2,500 peer-review manuscripts in high impact journals such as Pediatrics, JAMA, Circulation, and Cancer.* The CLSC program will support the TOTTS program's success in multiple ways. First, TOTTS trainees are required to complete coursework in ethics, RCR and GCP, CTR study design, and translational methodologies. Second, most trainees identify in their Individual Career Development Plan (ICDP) the need for additional coursework,

such as *Conducting Clinical Trials for Investigators, Dissemination and Implementation in Health Research, Critical Appraisal or Clinical and Health Outcomes and Applications.*

6. CCTSI's Leadership for Innovative Team Science (LITeS) program will be adapted for the TOTTS program (described in section B.3.2.1a below**).** LITeS, created at CU-D in 2009, is a leadership-training program tailored for senior scientists emphasizing skills for leading a team. LITeS provides didactic and experiential work to build the foundation for leadership skills in 3 domains: understanding of self, relationships with others, and executing work goals. Since 2012, LITeS has been led by Judith Albino, PhD, president emerita of the University of Colorado, Professor in the Colorado School of Public Health, and PI for a NIDCR-funded center focused on oral health disparities of American Indians. As a psychologist trained in executive coaching with extensive experience in academic leadership and organizational consulting, she is an asset to the program. Susan Johnson, PhD, Professor of Pediatric Medicine, and a LITeS alumna, is Associate Director of the program. Drs. Albino and Johnson provide much of the training. Evaluative efforts reveal that over half of participants apply their learning a great deal of the time, especially in managing interpersonal dynamics and within research teams. Over 70% reported enhanced social capital, an expanded network and increased connectedness to the institution as a result of the program. To develop leadership and team skills for TOTTS trainees, a LITeS Jr program will be developed and provided based off this successful leadership and team science program (described in section B.3.2.1a below**)**.

7. CCTSI's Community Engagement and Research Core builds on a rich history of practice- and community-based research in the state, which now includes 18 established community-academic partnerships and the State Network of Colorado Ambulatory Practices and Partners, a practice-based research network. Partnering communities include rural and urban populations, American Indian and Alaska Native, Hispanic and African American groups that provide a unique opportunity for research emphasizing health disparities. The innovative Partnership of Academicians and Communities for Translation Council brings academics and communities into a collaborative group for bidirectional exchange, fostering public trust in the research enterprise. Community liaisons from this core will be involved in TOTTS seminars related to developing partnerships, community engaged research and for facilitating community partner introductions.

This flourishing educational system will support the TOTTS to teach fundamentals of translational research, create a culture of team-oriented science, provide essential resources to junior investigators, and instill regulatory and dissemination skills. During the next funding period, we will continue to transform the educational landscape across the CCTSI community to ensure that our TOTTS trainees will thrive, develop skills, and remain persistent and successful in CTR.

A.5. Preliminary Data

CU-D Trainees. Over the first 7 years of our TL1 Research Training program, we received applications from diverse PhD programs, with an acceptance rate into the TL1 program of 28-40% (Refer to **Table 1**). Our original TL1 program focused on biomedical pre-doctoral trainees and trained 51 scholars representing 17 different PhD-granting programs. To date our efforts are effective and successful in many ways (See **Table 2**)- **86% of alumni are persistent in CTR and have published 222 original peer reviewed manuscripts**. Of our alumni that remain persistent or currently active in CTR, 64% are women, 5% are URMs, and 7% report disabilities (Refer to **Table 2**). Most (66%) alumni are currently completing post-doctoral training in CTR, 25% are working in industry engaged in CTR and 9% have launched their CTR career as faculty in academic settings. Of those not currently engaged in CTR, 68% are medical trainees/fellows. Positive feedback is overwhelmingly received from alumni and highlights the added value of the CCTSI TL1 program to their career. A survey of alumni completed in February 2017 revealed that participation in the TL1 program was pivotal to the establishment, pursuit, and achievement of CTR career goals. On a 5-point scale (with 5 being the highest level), a mean score of 4.6 was received for the importance of the TL1 program in pursuing a CTR career.

Table 1: TL1 Applicant Characteristics

Cohort yr	Applicants	URM	PhD program
2015-16	20	2	Bioeng, cancer biology, computational biology, human genetics, immunology, microbio, neuroscience, pharmacology, toxicology
2014-15	20	1	Bioeng, cancer biol, human genetics, immunology, integrated physiology, microbio, molec bio, pharmacology, toxicology
2013-14	27	2	Bioeng, cancer bio, epidemiology, immunology, microbio, neuroscience, human genetics, molec bio, reproductive science, pharmacology

2012-13	28	3	Bioeng, biomedical science, cancer bio, devt bio, human genetics, immunology, molec bio, neuroscience, pharmaceutical science, pharmacology
2011-12	27	3	Biochem, cancer bio, devt bio, clin health psych, immunology, human genetics, molec bio, pharmacology, microbio, neuroscience, reproductive science, pharmaceutical science
2010-11	28	3	Biochem,,Bioeng, biomedical science, cancer bio, devt bio, human genetics, immunology, molec bio, neuroscience, pharmaceutical science, pharmacology
2009-10	10		Cancer bio, immunology, microbio, neuroscience, human genetics, molec bio, reproductive science

Table 2: Metrics for TL1 Training Program Enrollees that Persist in CTR

Cohort	Engaged in CTR (#, %)	URM (#,%)	Women (#, %)	Disability (#, %)	Publica-tions (#)
2015-16 (n=8)	8 (100%)	1 (13%)	6 (75%)	1 (13%)	6
2014-15 (n=8)	6 (75%)	1 (17%)	2 (33%)	0	17
2013-14 (n=8)	7 (88%)	0	5 (71%)	1 (14%)	24
2012-13 (n=8)	6 (75%)	0	4 (67%)	0	43
2011-12 (n=7)	5 (71%)	0	4 (80%)	0	45
2010-11 (n=8)	7 (87%)	0	6 (86%)	1 (14%)	58
2009-10 (n=4)	3 (75%)	0	0	0	29
TOTAL 51	**42 (86%)**	**5%**	**64%**	**7%**	**222 (5)**

Table 3: Examples of Positions Held by TL1 Alumni

Post-Doctoral Research Fellow conducting CTR: Washington University, Stanford University, University of Minnesota, Case Western Reserve
Assistant Professor, CU-D Physical Therapy Program
Senior Scientist at Novartis
Sr. Medical Science Liaison II, Hematology - Shire
Cognitive Solutions Executive - IBM Watson Health
Principal Clinical Research Specialist - Medtronic
Scientist - Thrive Bioscience, Inc.

The most impactful aspects of the program were inclusion of a clinical mentor for PhD biomedical trainees and additional research activities and coursework. Below are two vignettes highlighting the trainees' perspectives.

Alumni Vignette 1: The TL1 program definitely made me want to do translational research for my career. Essentially, I'm still doing that now. It really solidified that … Even though translational biology is very challenging, I know that's exactly what I want to do … The TL1 program made translational work really important to me. From the program, I saw how useful and how powerful that research can be if you just slightly change directions or open up the scope to include…more translational [aspects].

Alumni Vignette 2: Because of the TL1 program, I was able to keep in mind that broader perspective of constantly applying my research to a human disease. A lot of my peers were pretty focused on their mouse model, or their gene of interest, or disease signaling pathway, or development process. [For me,] being able to keep the clinical translation in mind throughout the PhD process, rather than just thinking about it at the very end when you're writing your dissertation… [was] an opportunity to connect the dots along the way ... Now, as I'm trying to move my basic research to have more of a clinical arm, I have a better understanding of how IRB protocols work, and how I might need to get something like that approved. Having a better understanding of that world—how I can translate my basic science research to that world and vice versa—is really important in this day and age.

CSU Veterinary Scientists: Based on CSU's CVMBS experience with their T32 "Biomedical Research Training for Veterinarians" initially funded in 2003, 25 fellows have received training. They have authored 91 publications, representing 4.3 publications per trainee, including 43 first authorship peer-reviewed manuscripts. Seventeen of 20 alumni **(85%) persist in conducting clinical/translational research** and **35% (n=7) have received NIH Career Development awards**. In the current selections cycle, 7 outstanding candidates were considered for 2 slots and would have qualified for the proposed TOTTS program due to the nature of their translational research topics (e.g., cancer, reproductive physiology, viral evolution, antimicrobial resistance, pathogen discovery, mucosal immunology). Over 35 DVM graduate students and postdoctoral fellows have pursued research experiences at CU-D, similar to those proposed in TOTTS, for exposure to human clinical research and application of One Health principles. Both CSU faculty and trainees have taken courses or completed graduate degrees in CU-D's CLSC program. Taken together this demonstrates an unmet demand for CTR training among veterinarians and that it is now time to formalize the relationship between CSU CTR researchers and CU-D training programs. The proposed program will allow development of a unique CTR workforce of veterinary clinician scientists and directly addresses the short supply of such investigators identified in the NIH Physician Scientist Workforce report.[1] Our TOTTs trainees will be provided an exceptional opportunity to investigate the linkage between naturally occurring diseases in animals with analogous diseases in humans. An area identified for improvement and targeted activity is to attract, recruit, admit and retain URM trainees. This is a priority for the proposed application and is described in more detail in Sections B5..1.1 and C below.

B. PROGRAM PLAN

The overall objective of TOTTS is to enhance our capacity to train exceptional individuals in team-based clinical-translational science across the pre-clinical to population health spectrum and to leverage our minority pipeline (See below Section C), to ultimately build a diverse workforce. We are requesting 15 slots for our TOTTS program to train and prepare biomedical doctoral students, health care clinicians completing their professional doctoral training, post-doctoral medical residents (x2), and veterinary post-doctoral trainees (x4) pursuing careers in CTR. Consistent with our priority of infusing diversity into TOTTS, we are targeting a goal of 25-30% URM trainees. Trainees will receive 1 year stipend support, and in return, commit to completing the remaining requirements for their degree program (if applicable) and required elements of TOTTS. Our **Specific Aims** are:

CSU Vignette: As Director of Clinical Trials at CSU Flint Animal Cancer Center, I oversee the conduct of clinical trials involving client-owned dogs and cats with cancer and help investigators design and conduct oncology studies. As training in clinical trials and research is not something provided within a standard veterinary medical education, I pursued the Master's degree in Clinical Sciences, at CU-D AMC. This program not only provided didactic training in clinical and translational research, but also gave me exposure to the practices of human clinical research. As a result of this training and exposure, I have implemented changes in our system to improve efficiency, rigor and success. My training allowed me to form relationships with colleagues that are beneficial both to the veterinary and human realms of clinical research.

Specific Aim 1: Provide rigorous training that builds core competencies in clinical and translational research to become successful translational researchers.

Specific Aim 2: Mentor trainees using individualized career coaching and a multi-disciplinary team approach to provide experiences and perspectives in the conduct of translational research across the study lifespan and translational spectrum.

Specific Aim 3: Support the future success of trainees through integration into the clinical and translational science community and dissemination of scholarly products while building a scholarly portfolio.

Our overarching theme, Diversity in Accelerating Research Excellence (DARE) in CTR, will be integrated into our program and activities. First, we are targeting a 25-30% proportion of URM trainees. This will be accomplished by improving our marketing and recruitment efforts, integrating our marketing and recruitment efforts with the offices of diversity at the School of Medicine and the Graduate School, and leveraging the summer undergraduate research programs in the sciences and health professions. Second, we will be training our Recruitment and Selections Committee on reviewing applications in a holistic manner to calibrate the committee in terms of expectations, assessment, heuristics and weighting. Third, URM trainees will have an assigned URM mentor to provide contextualized support and personal experiences that those from dis-advantaged backgrounds may experience such as negative messages, self-doubt, and a dearth of URM role models. URM mentors will provide opportunities and guidance so trainees experience accomplishments and the concomitant sense of agency achieved as part of the personal/professional growth process. Fourth, in addition to activities for trainees, we will integrate diversity into our CCTSI educational system and infrastructure, which includes weaving the following topics into CO-Mentor and LITeS programs: holistic review of applications/dossiers, unconscious bias, importance and team work of diverse teams, and effective mentorship for diverse mentees. Fifth, through our Leadership Advisory Council and the CCTSI Executive Committee we will advocate for institutional policies to alleviate environmental pull factors, influence partners in providing continuity of support for trainees and foster an environment for effective mentorship and peer support to promote academic and social integration. These activities are congruent and supportive of our conceptual model, Achieving Persistence in a Diverse Clinical and Translational Research Workforce.

B.1 Program Administration (See **Figure 2** for an illustration of TOTTS' organizational structure.)

B.1.1 Program Directors. **Lisa Cicutto RN, ACNP(cert), PhD** will serve as TOTTS director and provide overall program and budget oversight. She will oversee the directors for each target group of trainees. (Refer to **Table 4** for a complete list of roles for directors). In 2016 she was appointed director of the CCTSI's Translational Workforce Development Core and has directed the Clinical Science Graduate Program since 2008. She is a member on the national CTSA Workforce Development Domain Task Force, which will now include TL1 Program Directors (Decided at May 2017 meeting). She is collaborating with the Southern California CTSI (site PI) to identify best practices for Individualized Development Plans. At National Jewish Health, she is Director, Community Outreach and Research. Her research focuses on developing, evaluating, disseminating and implementing innovative best practice programs to improve health of people living with lung conditions by partnering with health providers and individuals and families. She holds active EPA and Colorado Department

of Health funding to improve the health of those with lung conditions living in rural and environmental justice communities. She has held consistent external funding as a Principal Investigator since 1998. Her passion is to work with, mentor and train future scientists to answer important patient/public health oriented questions that are subsequently translated to patients/people living in their communities. She has served in key roles and capacities for over 45 students related to their research. Program Administration will include Dr. Cicutto plus four Associate Directors according to the following programmatic targeted trainees:

Doctoral Student Biomedical trainees **John Tentler, PhD** is an Associate Professor in the Department of Medicine, Division of Medical Oncology and a Senior Scientist in the Program for the Evaluation of Targeted Therapeutics. He has served as the TL1 Program Director for the past four years and will continue to be the director for the PhD student biomedical trainees. Dr. Tentler is a translational scientist with over 15 years of experience performing pre-clinical lab-based studies with the ultimate goal of translating findings to patient care through clinical trials. His work involves several cancer types including breast, colon, pancreatic, and skin. Dr. Tentler is active in medical and biomedical education and is the recipient of teaching and mentoring awards. He has served as a research mentor for 12 PhD students and 10 post-doctoral fellows. Since 2013, Dr. Tentler has been a member of the national TL1 Pre-Doctoral Committee.

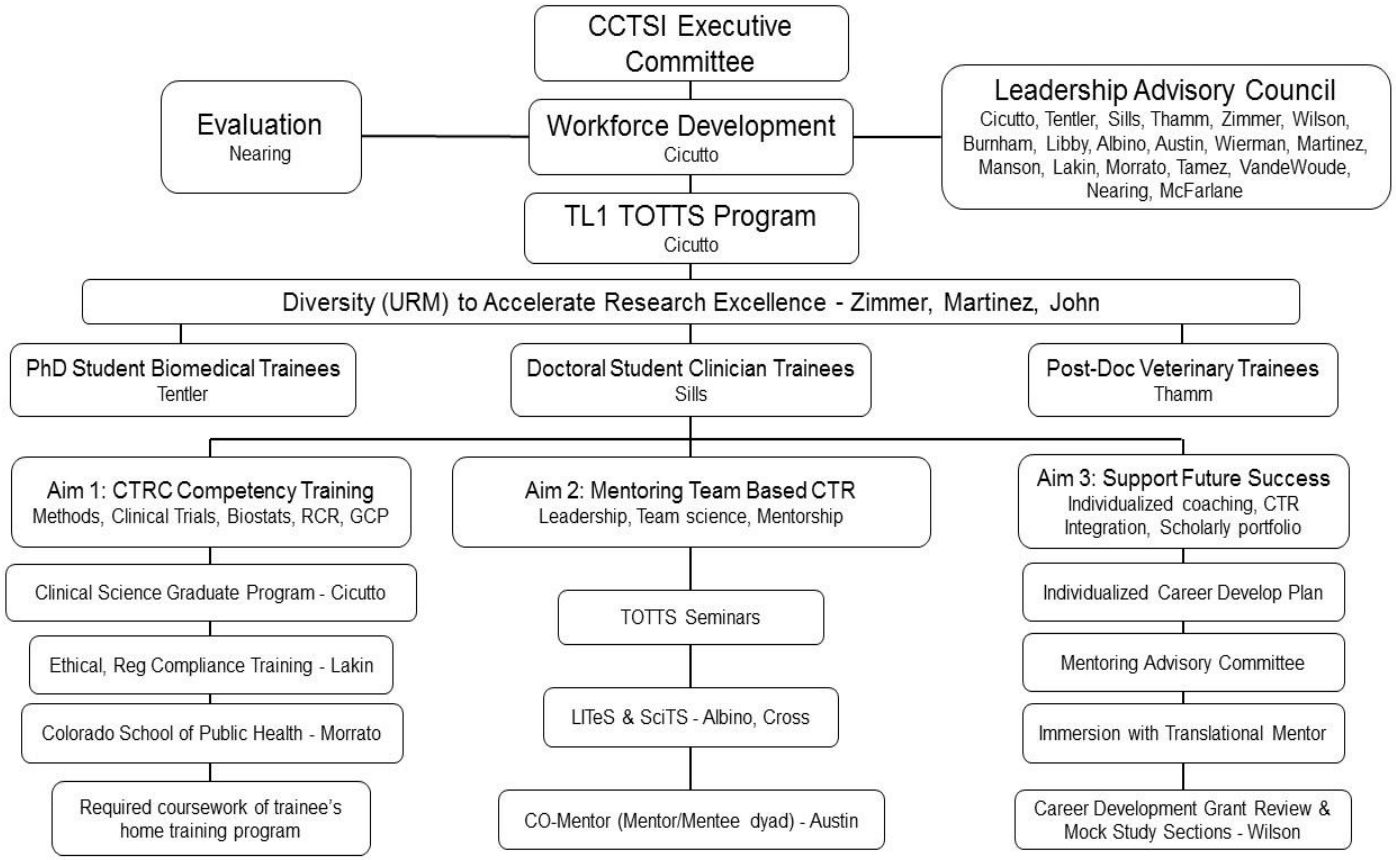
Doctoral Student Clinician trainees: **Marion Sills, MD, MPH** is a Professor of Pediatrics and Emergency Medicine and a T3/T4 translational scientist with over 20 years of direct patient-care experience. She conducts health services research related to primary and emergency care delivery for children and is an investigator with Adult and Child Consortium for Health Outcomes Research and Delivery Science (ACCORDS) program. Currently, she is funded to study the impact of primary care delivery system redesign on asthma outcomes. She is a primary mentor in CU-D's Emergency Medicine Scientist Training and Mentorship Program developed to foster career development of junior physician scientists and mid-career mentors. She has served as a research mentor for 7 faculty, 1 subspecialty fellow, 1 PhD student and 2 MSPH students. She has provided intensive, bedside clinical teaching to 2,900 medical trainees and fellows. Starting in 2014, she co-directed the previous TL1 program and assisted biomedical trainees with identifying clinical mentors and experiences. With our new proposed TOTTS program, she will continue to assist trainees in identifying clinical immersion experiences and will serve as the TOTTS program mentor for clinician trainees (pre- and post-doctoral).

Veterinary Post-doctoral trainees: **Douglas Thamm, VMD, DACVIM (Oncology) at CSU** will oversee TOTTS training at CSU for veterinary medicine trainees, a new targeted group of trainees for this application. He is the Barbara Cox Anthony Professor of Oncology and Director of Clinical Research at Flint Animal Cancer Center, overseeing the Clinical Trials Program in addition to running a NIH funded translational lab dedicated to exploring novel therapeutics and therapeutic combinations in human and animal cancer models and providing pharmacodynamic support for ongoing clinical cancer trials. Dr. Thamm has served as primary mentor for 13 PhD and DVM/PhD students and as committee member for an additional 31 graduate students. He has served on the DVM/PhD selection committee since 2011. His extensive research and mentoring experience and commitment to post-DVM graduate education and research will provide strong leadership for TOTTS.

URM Leader/Mentors: **Shanta Zimmer MD** is the Associate Dean for Diversity and Inclusion at the School of Medicine. Since 2010, she has been actively engaged in creating a culture that views diversity as a strength. At the University of Pittsburgh, she served as director of the translational track within the education core of the CTSI and then developed initiatives for enhancing diversity in graduate medical education when she served as the residency program director for internal medicine. She was recruited to UCD in 2016 because of her expertise and success in enhancing the diversity of the physician workforce through targeted diversity recruitment, retention and mentorship programs. She is a co-investigator on a NIH funded project focused on professional skill development for mentors. She is an infectious diseases physician interested in vaccinology and respiratory viral transmission. In her TOTTS role, Dr. Zimmer will attend TL1 Program Administration and Leadership Advisory Council meetings, serve as a URM mentor for TL1 program trainees, provide direction and guidance into the TL1 program curriculum as well as the overall curricula for the CCTSI Workforce Development Core, collaborate with program directors of CO-Mentor and LITeS to integrate topics into the curriculum that support a culture of diversity to accelerate research excellence (such as micro-aggressions, mentoring a URM), provide workshops to Recruitment and Selections Committees on reviewing applications in a holistic manner, and serve as the bridge to the SOM's Office of Diversity and Inclusion and other campus initiatives for attracting and recruiting URMs to our campus. To assist Dr. Zimmer and be readily available on campus for CSU trainees, **Gilbert John PhD,** will serve as the CSU URM mentor with his effort being in-kind (**See Biosketch**). Dr. John is Assistant Dean of Research in the CVMBS and Director of Diversity and Inclusion at CSU. Dr. Gilbert recently returned to CSU after 15 years in the Department of Microbiology and Molecular Genetics at Oklahoma State

University. Dr. John received his doctorate and undergraduate degrees from CSU and is a first generation college graduate from the Navajo Nation. He has extensive experience in successfully developing programs for URMs and is dedicated to diversity and inclusion.

Figure 2: Organizational Chart of the TL1 Program



Please refer to **Table 4** for a list of activities that will be completed by the directors. A major role of directors is to provide individualized coaching, mentoring and advice to address environmental pull factors experienced by the trainee, such as competing or conflicting demands, integration into projects and teams, and navigating institutional obstacles and challenges. Additionally, directors will advocate for institutional policies to alleviate environmental pull factors by creating a culture of team science and that with diversity there is strength.

Galit Mankin, BA, MSW will be the TOTTS Program Administrator. She has worked at CU-D since 1998 and for the last 8 years has served and will continue as Program Administrator for the Clinical Science Program. She became the Program Administrator for the CCTSI Workforce Development Core in 2016. She has extensive experience developing relationships with trainees to provide guidance and advice for succeeding in training programs. Ms. Mankin will work closely with Directors in coordinating recruitment and selection of new trainees; tracking and reporting records for trainees to ensure compliance with NIH guidelines/regulations (such as Good Clinical Practice and Responsible Conduct of Research training); application of xTrain system; and collecting and compiling annual progress reports.

B.1.2. Organization and Structure

The leadership structure of the TOTTS TL1 Program consists of (1) a Leadership Advisory Committee to oversee and provide program guidance, (2) 4 programmatic Associate Directors (described above B.1.1) who report to the overall Program Director (Cicutto), and (3) a Recruitment and Selection Committee to support these key operational activities. The **Leadership Advisory Committee** will meet monthly, be chaired by Lisa Cicutto RN, PhD (TOTTS PI/Program Director and Director Workforce Development and CLSC), and consist of all TOTTS Associate Directors (Tentler, Sills, Zimmer, Thamm), Dominic Martinez PhD (Senior Director, Office of Inclusion and Outreach), Gregory Austin MD (Director, CO-Mentor), Cara Wilson MD (DOM Vice Chair Faculty Development, KL2 Co-Director, and Director Career Development Grant Review Program), Arthur McFarlane III MPH (Population Health Analyst, great-grandson of American civil rights-activist W.E.B. Du Bois

Table 4: Program Administration Roles
• Attend and receive counsel at monthly Leadership Advisory Committee meetings
• Trainee selection process: answer applicant questions, assist trainees/applicants in matching with faculty mentors, review applications, conduct interview with finalists
• Curriculum oversight
• Organize and participate in bi-monthly TOTTS Team Science and Leadership Seminars
• Trainee advising and mentoring: Review and update ICDP every 3 months, review manuscripts & proposals, provide career development advice and support management of environmental pull factors
• Work to attract and maintain diverse trainees and create a environment of excellence through diversity
• Ensure trainee is current with GCP, RCR and other required regulatory training
• Faculty Review: Meet with mentors and mentees to ensure research and scholarly productivity and, if necessary, resolve conflict
• Program Evaluation: Every 6 months review and apply data and feedback to enhance program

member, Colorado Equal Opportunity Coalition), Judith Albino PhD (Director, LITeS and Center for Native Oral Health Center), Montelle Tamez MPH (CCTSI Community Engagement Core), Spero Manson PhD, Distinguished Professor of Public Health and Psychiatry (directs the Centers for American Indian and Alaska Native Health with partnering relationships with the university's URM pipeline), and Sue VandeWoude DVM, DACLAM (CSU's CVMBS Associate Dean for Research; Member, CCTSI Executive Committee and serves as a member on several national committees focused on veterinary translational research training programs). The role of this committee is to (a) provide overall guidance and oversight of TOTTS in providing the best possible program for trainees, (b) review and approve applicants selected by the Recruitment and Selection Committee, (c) ensure integration for successful multidisciplinary training activities, dialogue, and team socialization across the translational spectrum, (d) assist with review of training initiatives and mapping to NIH CTR core competencies, (e) monitor program metrics and inform ongoing evaluative efforts, and (f) program promotion across the CCTSI and to CTSA hubs. A focus of monthly meetings will be to identify potential trainees who are URMs that may be approached by TOTTS leadership to ensure their awareness of the program and to provide coaching and resources to compete successfully for this award. The Recruitment and Selection Committee will review and refine recruitment strategies to aggressively recruit top candidates from diverse backgrounds, answer potential applicant questions, holistically review applications, perform applicant interviews with mentors for top applicants, make selection recommendations, and provide applicant feedback. Members of the Recruitment and Selections committee will serve 5 years. The chair (Tentler) will solicit new members as needed with the intent of maintaining balance regarding faculty sector, gender, diversity and seniority.

B.2. Program Faculty

We have a talented and experienced group of potential CU-D faculty mentors for the TOTTS TL1 trainees. (**Table 5** provides a representative sample**)** All are accomplished CTR investigators and have a track record of success in training new investigators. Mentors will have sufficient funding to cover costs of their trainee's research. Listed investigators demonstrate diversity in our mentoring pool regarding areas of research, institution, funding source, and mentoring experience. Demonstrating the numerous broad spectrum of mentoring opportunities, w*e did not include mentors from the CCTSI leadership in Table 5,* who will also be available to trainees**.** Our faculty pool is fluid in that trainees identify mentors (research and translational) in their TL1 application. If an applicant does not have a defined mentor, the Program Administration will assist the applicant in choosing a mentor. The strength of the mentor/mentoring team is a criterion scored in the application review process. All mentors of awarded TOTTS trainees will be vetted by Program Administration to ensure they: 1) demonstrate a deep commitment to training junior investigators; 2) demonstrate excellence in their track record for mentoring junior investigators; and 3) are actively involved in CTR with research funding. If gaps are identified with the proposed mentoring team, Program Administration will work with the mentor and mentee to identify an additional senior mentor. There may be times when a mentor may change institutions, or need to be removed from the program for various reasons such as conflicts of interests, personality clashes, lack of commitment, time and/or resources. Program Administration will carefully monitor the evaluations of mentors in conjunction with ICDPs, and will arbitrate the removal of a mentor if necessary. Should this occur, Program Administration will assist the trainee to find an appropriate substitute.

Table 5. Representative CU-Denver Mentors for TL1 Program

Mentor	Institution	Department or Training Program	Area of Research Expertise	Research Funding	Pre/post docs
Rafael Alam, MD, PhD	CU-D NJH	Allergy and Immunology	Mechanism of persistence of inflammation in asthma	R01 x 2	7/41

Peter Anderson, Pharm D, PhD	CU-D SOP	Pharmacy	Optimize drug therapy in humans	R01 x 2, U01, UM1 x 2	10/5
Bruce Appel, PhD	CU-D SOM	Pediatrics	Degenerative, and cancerous diseases of nervous system	R01 x 3	17/17
Jeffrey Bennett, MD, PhD	CU-D SOM	Neurology	Neuro-immunology	R01, Gunthy Jackson Charitable Fnd. award x 2	2/5
Cathy Bodine, SLP, PhD	CU-D SOE	Bioengineering	Assistive and mainstream technology for persons with disabilities	Rehab Engineering Research, State Grant	20/2
Virginia Borges, MD	CU-D SOM	Medical Oncology	Pregnancy-associated breast cancer	R01, DOD x 2	14/8
Uwe Christians, MD, PhD	CU-D SOM	Anesthesiology	Toxicology	R01	33/0
Sean Colgan, PhD	CU-D SOM;	Integrated Immunology	Inflammatory Bowel Disease	R37, R01 x 2, VA	20/22
Kevin Deane, MD	CU-D SOM	Rheumatology	Genetic and environmental factors on the development of RA	UM1, U01	4/16
Robert Deobele, MD, PhD	CU-D SOM	Medical Oncology	Oncogenic gene fusions in lung cancer - ALK, ROS1, and RET	R01, P50, Threshold, Ignyta	7/12
Jorge DiPaola, MD	CU-D SOM	Pediatrics	Hemostatic system effects, on human disease including cancer	R01 x 3, UM1, T35	8/23
Tobias Eckle, MD, PhD	CU-D SOM	Endocrinology, Metabolism and Diabetes	Lipids in regulating energy balance, body weight, insulin, learning,	R01	26/12
Tasha Fingerlin, PhD	CU-D, NJH CSPH	Epidemiology & Biostatistics	Diabetes, Chronic Beryllium disease and Schizophrenia	R01 x 2	13/0
Jacob Friedman, PhD	UC-D SOM	Pediatrics	Maternal-Fetal Metabolism	R24, UG3, R01, P30, Bill and Melinda Gates	20/51
Emily Gibson, PhD	CU-D SOE	Bioengineering	Optical technologies for imaging activity and stimulation in living brain	CBET, NSF, NSF, DBI, P30	4/4
Ronald Gill, PhD	CU-D SOM; NJH	Immunology and Microbiology	Regulation of developmental genes	UC4, R01 x 2	15/13
Kirk Hansen, PhD	UC-D SOM	Biochemistry and Molecular Genetics	Involvement of proteins and metabolites in disease progression	R33, P50, DOD, Down's Syndrome Inst, R01	7/0
Lynn Heasley, PhD	UC-D SOM	Craniofacial Biology	Functional genomics for combination therapies targeting oncogenic pathways	P50 x 2, VA merit, Cancer League of Colorado	11/5
Michael Holers, MD	CU-D SOM; NJH	Immunology	Complement receptors and membrane regulatory proteins	R01, UM2, UH2, UM1, U01	7/30
Ed Janoff, MD	UC-D SOM	Infectious Disease	Mechanisms of humoral defense, against infection at mucosal sites	VA, R01 x 2	9/34
William Janssen, MD	UC-D SOM NJH	Pulmonary Medicine	Alveolar macrophages orchestrators of inflammation and phagocytes	DOD, R01 x 8	1/6
Peter Koch, PhD	CU-D SOM	Dermatology	Cell adhesion molecules	R56, P30	1/5
Paul Maclean, PhD	UC-D SOM	Endocrinology, Metabolism	Obesity and metabolic disease	R01 x 3, P30, P50	6/13
Ed Melanson, PhD	UC-D SOM	Metabolism and Diabetes	Effects of lifestyle interventions (on bioenergetics	R01, R01, P50, R44, R01	4/5
Thomas Morrison, PhD	CU-D SOM; NJH	Immunology and Microbiology	Regulation of innate immunity and response to bacterial infection	U19, R01 x 2	5/3
Karin Payne, PhD	CU-D SOM	Orthopedics	Optimizing differentiation of human stem cells for bone and cartilage regeneration	R03, AOSSM, Dept Ortho Pilot Res Award, Anschutz foundation	6/0
Dohun Pyeon, PhD	CU-D SOM; NJH	Immunology and Microbiology	HPV contribution to HPV--associated cancer progression	R01X2, Mary Kay, CCTSI, CO Cancer	6/3
Jennifer Richer PhD	UC-D SOM	Pathology	Steroid Hormone Receptors in Breast and Gynecological cancers	DOD x 3, P01 x 2, Amer Cancer Society	6/6
Carol Sartorius, PhD	UC-D SOM	Pathology	Role of estradiol and progesterone and their cognate receptors in the molecular therapy of breast cancer	R01 x 4, R21, Breast cancer res fnd, RNA biosciences grant	7/13

Jennifer Stevens-Lapsley, DPT, PhD	UC-D SOM	Physical Medicine and Rehabilitation	Clinical trials involving patients with total knee replacement (TKR)	R01 x 2, R56, VA Merit x 2, VA SPiRE	7/4
Jason Tregellas, PhD	CU-D SOM	Psychiatry	Neurobiology of food intake behaviors and obesity	VA, R01 x 2	1/3
Dennis Voelker, PhD	CU-D SOM, NJH	Biochemistry and Molecular Genetics	Lipid metabolism, lipid transport and lipid enzymology	U19, R01 x 2	2/34
Richard Weir, PhD	CU-D SOE	Bioengineering	Advanced prosthetic systems for individuals with limb loss	OT2, VA x 2, R01, R44	19/0

Specific to the mentoring faculty for the veterinary post-doctoral trainees, there are 51 CSU mentoring faculty representing all four CVMBS departments (**Table 6** displays a representative sample). Thirty-eight faculty included in this application currently mentor 82 pre-doctoral, 20 postdoctoral, and 104 DVM resident trainees. *They have collectively graduated 176 pre-doctorates; 129 of these (76%) continued in research careers. They have trained 282 postdoctoral fellows; 189 of these (67%) have continued in research related careers*. All mentoring faculty are current principal investigators; 40 are established mentors and 11 are junior mentors selected for their rising careers, research programs, and bright mentorship potential. Thirty of the 54 mentors direct programs funded in whole or part by NIH. Mentoring faculty possess expertise in infectious disease, RNA biology, cancer biology/therapy, reproductive biology, neuroscience, cardiovascular physiology, musculo-skeletal disease, nutrition/metabolic disease, immunology and stem cell biology. Research interests span the translational spectrum, including 20 faculty with primarily basic science interests, 25 with translational research interests, and 9 with predominantly veterinary clinical trials. Taken together, the faculty of mentors represent diversity in scientific specialty, age, gender, background and research expertise thereby allowing sufficient and varied opportunities for trainees to connect with the appropriate mentor. As mentioned above (Section B 1.1), Dr. John will serve as the URM mentor for all CSU veterinary TOTTS trainees.

Table 6. Representative CSU Mentors for Veterinary TL1 Trainees

Mentor	Department or Training Program	Area of Research Expertise	Funding Source	Pre/ post docs
Akkina,Ramesh, DVM, PhD	Microbiology, Immunology & Pathology	HIV and Dengue virus, gene and antimicrobial therapies in human stem cells	R01 x 3, 2 R01 subs	10/16
Amberg, Gregory, PhD, PharmD	Biomedical Sciences	Smooth muscle, endocrine, and vascular cell physiology	R01	3/2
Bailey, Susan, PhD	Environmental & Radiological Health	Telomere alterations relating to pathogenesis of aging, cancer, and radiation damage	NASA x 2	13/1
Basaraba, Randall, DVM, PhD	Microbiology, Immunology & Pathology	Pathogenesis of mycobacterial infections in laboratory animal models; synergism of tuberculosis and diabetes	R01, R21, U19 sub	4/7
Belisle, John, PhD	Microbiology, Immunology & Pathology	Mycobacterium tuberculosis Proteins, growth regulation, pathogenesis/immunization	U01, R21/33, R01	8/11
Bowen, Richard, DVM, PhD	Biomedical Sciences	Zoonotic infectious diseases, modeling, animal models	USDA x 3, USAID, DARPA, DTRA,	11/5
Dow, Steve, DVM, PhD	Clinical Sciences	Mucosal liposome-based vaccines and immune therapeutics,	CCTSI, Shipley Foundation, Merck	18/15
Ebel, Gregory, SM, ScD	Microbiology, Immunology & Pathology	Arboviral genetic diversity and adaptation to host and vectors	R01, R21 x 2, TDA Research Inc	6/6
Hentges, Shane, PhD	Biomedical Sciences	Neuronal function in energy balance regulation; opioid receptor function	R01 x 2	6/2
Hoover, Edward, DVM, PhD	Microbiology, Immunology & Pathology	Pathogenesis and intervention for retrovirus and prion infections	R01, T32, DOD, P01 sub	2/9
Lenaerts, Anne, PhD	Microbiology, Immunology & Pathology	Anti-tuberculosis drug discovery and anti-mycobacterial resistance;	NIH TO, Gates Foundation, Global Alliance for TB,	5/2
Magzamen, Sheryl, MPH, DVM	Environmental & Radiological Health	Environmental health science and chronic diseases	EPA, K22, NIEH	7/2
Reynolds, Stephen, PhD	Environmental & Radiological Health	Health effects of organic dusts, aerosols, and the microbiome	U54, T42 sub, U01	24/0
Ryan, Elizabeth, PhD	Environmental & Radiological Health	Interaction between food, gut microbial metabolism, and GI immunity and metabolism	R01, USDA, CancerCare	5/5
Santangelo, Kelly, DVM, PhD	Microbiology, Immunology & Pathology	Animal models of primary and secondary osteoarthritis	CCTSI pilot, CSU Research Funding	0/3

VandeWoude, Sue, DVM	Microbiology, Immunology & Pathology	Biology, pathogenesis, trans-species infectivity, and co-evolution of HIV-like retroviruses	R25, NSF, CCTSI sub, T32, T35, Morris Animal Foundation	6/17
Webb, Craig, DVM, PhD	Clinical Sciences	Oxidative stress and relationship to blood cell dysfunction in disease; gastrointestinal diseases	Comparative Gastroenterology Society, Royal Canine	12/0

Mentors will meet at least weekly with TOTTS trainees and oversee progress according to the trainee's Individual Career Development Plan (ICDP) for research, training, career development, including participation in the TOTTS Program. Research mentors will be responsible for ensuring that the trainee adheres to ethical and regulatory practices (including IRCR and GCP training, RB and IACUC approvals, when appropriate), and maintains research-training certificates.

Mentor Training. While we have outstanding faculty to mentor our TOTTS trainees, there are always areas for improvement and strengthening of mentorship skills. Growing evidence suggests that **successful mentoring involves formal training** in mentorship and leadership[29], based on this evidence and the call in the FOA for training mentors **to ensure successful guidance of trainees, mentors will be *required* to attend the Colorado Mentorship Program** (CO-Mentor; Described in Section B3.2.) for half-day quarterly workshops.

B.3. Proposed Training

TOTTS will provide funding for a full year to train and prepare biomedical PhD students, health care clinicians completing their professional doctoral training, post-doctoral medical residents (x2) and veterinary post-doctoral trainees (x4) pursuing careers in CTR. Consistent with our priority of infusing diversity into TOTTS, we are targeting goal of 25-30% URM trainees. TOTTS encompasses 7 core components (**Table 7),** based on our conceptual model of persistence in a diverse CTR workforce developed by colleagues, Nearing & Manson. [16-18]

Table 7: Alignment between TOTTS Program and our Model of Persistence in CTR

Program Elements	Persistence Factor Addressed
1. Individualized Career Development Plan (ICDP)	Formalized process for using the seamless pipeline to achieve individual's goals and milestones
2. Mentorship	Provide effective mentorship and peer support to promote academic and social integration
3. Individualized CTR Training	Supports ability to plan, conduct, and disseminate meaningful research
4. Research Project Supervision	Supports ability to plan, conduct, and disseminate meaningful research. Provide effective mentorship to promote academic and CTR integration
5. TOTTS Seminars	Advocating for self and managing environmental pull factors and Promotes academic and social integration into CTR
6. Immersion Experience with Translational Mentor	Promotes academic and social integration into CTR
7. Translation of CTR	Promotes academic and social integration into CTR

Individualized Career Development Plans (ICDP) and **Mentorship** play central roles in the developmental process of trainees[16-18]. Therefore, all trainees will complete an ICDP within the first month of starting the program that outlines their short and long-term objectives and resources and activities required to meet objectives. Program Administration and the trainee's mentors will assist with the development and review of the ICDP. Each trainee will have a **Mentor Advisory Committee (MAC)** comprised of at least 3 mentors: TOTTS Associate Directors/ Director, research mentor, and translational mentor, although the committee composition will vary to meet the contextual and developmental needs of the trainee. The PhD biomedical trainees' MAC will include John Tentler PhD, the trainee's research mentor from his/her doctoral program, and a clinician mentor with similar research interests of the trainee who will serve as the translational mentor. It is anticipated that each biomedical PhD trainee will have a thesis committee formed that will have overlap in committee membership for the research mentor and the translational mentor. This model worked well for trainees based on our previous TL1 program experience. For clinical trainees, the MAC will consist of Marion Sills MD, MPH, serving as TOTTS mentor, the research mentor, and a translational mentor who will be active in community engaged research, policy research or in a biomedical lab researching an area complimentary to the trainee's research focus. The Veterinary Post-Doctoral trainees' MAC will include Doug Thamm PhD, DVM, the research faculty mentor and a human clinical and translational researcher with a similar research interest. For TOTTs trainees that are URMs, they will benefit from the addition of a URM mentor (Shanta Zimmer MD or Gilbert John PhD) to their MAC. The ICDP will include sections for identifying learning needs/gaps, proposed activities to close learning gaps (including course requirements), translational activities, immersion experiences with translational mentor, milestones (presentations, publications, grant planning, research project defenses, etc.) and a corresponding timeline. Planning out activities with timelines is an essential skill and necessary for

navigating the complex landscape of CTR as an investigator. Trainees will provide monthly ICDP updates to MACs. Remaining programmatic core components will be discussed below according to our **Specific Aims**.

Program Specific Aims:

B. 3.1 Specific Aim 1: Provide rigorous training that builds core competencies in clinical and translational research to become successful translational researchers.

Trainees will be provided funds to obtain formalized coursework specific to the needs of each trainee. All TOTTS trainees will take courses in translational science methods (biostatistics, study design), ethics and responsible conduct of research including Good Clinical Practice (Described in Section D), and human and health systems. As described above (B.3), each trainee will have a MAC that will work with the trainee to develop an ICDP that identifies specific learning needs/gaps and the corresponding courses/ educational initiatives to close the gaps, as well as coursework necessary to fulfill the degree, if appropriate. **Table 8** lists courses to be completed by TOTTS trainees over the one year according to targeted stream and fulfills the requirements for obtaining a Certificate in Clinical Science. It is anticipated that clinician doctoral students and medical residents will add a year onto their timeline for completing their professional doctorate or residency. In essence they will be completing a gap year to pursue formalized training in CTR through TOTTS. All coursework completed during TOTTS (20 required course credits and 4 credit hours for tailored electives) may be applied to fulfill degree requirements for the Masters of Clinical Science (30 credit hours of which 4-6 credit hours are research publishable paper credits). Although it is unlikely trainees would complete the degree in the 1 year (3 semesters) of TOTTS, it could be completed in one additional term.

Table 8: Proposed Courses for TOTTS Trainees According to Targeted Stream

Clinical Doctoral Students/MD Residents	Biomedical Doctoral Students	Veterinary Post-Doctoral
Applied Biostatistics I and II (CSPH)	Biostatistics (CSPH)	Biostatistics (CSU)
Study design: Epidemiology and Design AND Conduct of Clinical Trials (CLSC, CSPH)	Study design: Epidemiology or Design and Conduct of Clinical Trials (CLSC, CSPH)	Study design: Epidemiology or Design and Conduct of Clinical Trials (CLSC, CSPH)
Critical Appraisal of CTR Studies (CLSC)	Human Disease/Systems (Home program)	Translational Biomedical Research and Animal Models Selection (CSU)
Conducting Clinical Trials for Investigators (CLSC)	Biology/Health System (Home program)	Writing Scientific Manuscripts and Grants (CSU) (Participation in Career Development Grant Review and Mock Study Section; see B.3.3)
Ethics and Responsible Conduct of Research (CLSC)	Ethics and Responsible Conduct of Research (CLSC)	Ethics and Responsible Conduct of Research (CLSC)
Clinical and Health Outcomes (CLSC)	Home Program requirement	Grant Writing (CLSC)

CLSC-Clinical Science Program CSPH-Colorado School of Public Health CSU-Colorado State University

B. 3.2 Specific Aim 2: Mentor trainees using individualized career coaching and a multi-disciplinary team approach to provide experiences and perspectives in the conduct of translational research across the study life span and translational spectrum.

Highly effective and productive teams consist of members that are skilled leaders, builders of relationships, share common goals for impactful work, make time for humor, and communicate proactively while having structure and clarity for their work[30-33]. When a team has a culture of leadership, it is not about multiple team members trying to be the leader, it is about the team owning its work and supporting each other because they want the team to be more successful than any one individual. The principles and skills for effective teamwork cross into the arena of effective mentoring. Both rely on building relationships, sharing common goals and working towards them, and communicating proactively. Therefore, our program will build these skills among TOTTS trainees and their mentors through two programmatic elements, TOTTS Seminars and CO-Mentor.

B.3.2.1. TOTTS Seminars The goal of these seminars is to develop skills aligned with the NIH CTR core competencies and that promote a successful and sustained team oriented translational research career. All TOTTS trainees will attend twice monthly 4-hour Seminars. Activities and topics include discussing research issues from a T0.5 to T4 perspective, leadership, working in teams and conducting team oriented science, entrepreneurship, working in communities, translating research across target audiences (patients, citizens, researchers, clinicians, funders, and policy makers), and providing opportunities for networking. Examples of presenters include Leslie Wright from Kaiser Permanente and the Community Engagement Core discussing Diversity/Cultural Competency; Dr. Reginaldo Garcia, a community liaison in the Community Engagement Core discussing community engaged research and partnering with community; Dr. Marilyn Greenwalt, RKS Core discussing challenges in performing large clinical trials, and Dr. Doug Thamm from CSU outlining the process and criteria for selecting animal models in CTR. In addition, each TOTTS trainee will present with his/her mentees

on their general research focus in a format that facilitates discussion across the CTR spectrum. Real-life examples will be used to familiarize trainees with the development and conduct of team oriented CTR, the challenges and benefits, and approaches to translating research from bench to clinic to community. Additionally, a separate curriculum focusing on skill development in team functioning and team oriented research and leadership will be integrated into these twice-monthly seminars described below.

B.3.2.1a. Science of Team Science (SciTS) and Leadership in Innovative Team Science (LITeS) will be integrated into TOTTS seminars. **SciTS** is a new curriculum to catalyze and develop interdisciplinary teams. It addresses the shift in science from an individual-based to a teamwork model. **LITeS** was initially developed and offered to more senior leaders within the CCTSI and university however, because of its success, we will be integrating it into TOTTS seminars as LITeS Jr. A LITeS Jr. version will be developed to appreciate and address the different developmental career stage of trainees. Specific concepts discussed will include emotional intelligence, leadership qualities, communication skills, making time for humor, and understanding the importance of diversity in highly functioning teams. In addition, Drs. Zimmer (SOM Office of Diversity and Inclusion) and Martinez (Office of Inclusion and Outreach; See Biosketches) will enhance training content to include sessions addressing unconscious bias, microaggressions, and development of diverse teams. These sessions will be also be added to LITeS to build leadership skills that support creating a culture that values diversity as a necessity for excellence and team science. SciTS and LITeS workshops will be scaled up and are based on activities first developed and evaluated at CSU for SciTS (**see Component C. Community and Collaboration**) and the CCTSI's for LITeS (described in section A.4 Infrastructure). Jeni Cross PhD (CSU-SciTS; See Biosketch) and Judith Albino PhD (LITeS, CU-D; See Biosketch) are directing faculty for these offerings and will identify additional faculty for TOTTS workshops.

B.3.2.2. Mentorship positively influences academic productivity, feelings of self-efficacy, job satisfaction, and career development[34-37]. Mentees with influential and sustained research mentoring are more likely to remain in research, publish more papers, become principal investigators, and mentor others[38]. The CCTSI and our TOTTS program are committed to providing excellent mentorship to our trainees and their mentors. As formalized efforts to improve the skills of our TL1 mentors, we will require mentors to complete a mentoring program, CO-Mentor, with their mentee. Members of our CCTSI team have been leaders in professional development programs to build skills in mentoring at a national level[39-43].

Because studies suggest that mentors and mentees benefit from a formal, structured training program to enhance the mentor-mentee relationship[38, 40-43], we created a novel mentor-mentee mentoring program, CO-Mentor, with Gregory Austin MD, MPH the Director and Anne Libby, PhD the Associate Director. CO-Mentor's aims are to: 1) develop skills and behaviors consistent with effective mentoring relationships; 2) enhance the specific mentor-mentee relationship; and 3) build a network of trained mentors and mentees who could model these practices for others, leading to a sustainable culture of mentoring at CCTSI institutions. By ensuring that TOTTS trainees and their mentors have free access to CO-Mentor, our CCTSI is supporting the growth of a solid mentor-mentee relationship that is critical to mentee success and a culture of team science.

CO-Mentor will consist of 4 half-day sessions, occurring every 7 weeks. Session 1 will focus on career mapping skills and interpersonal communication skills. The CVs of mentors and mentees will be reviewed to highlight whether an individual's career goals are appropriately reflected. These interactive self-knowledge and communication skill-building activities build the foundation for enhancing mentoring outcomes. Session 2 will split mentors and mentees. Mentees will have interactive discussions on "Creating and Managing Your Personal Board of Directors" that focus on how to build a comprehensive mentoring team. Attention is focused on how mentees can optimize these relationships by knowing their needs and communicating expectations to their mentors. Separately, mentors will discuss techniques to give and receive feedback from mentees. Before the next session, mentees will review mentoring team gaps with their mentors and formulate a plan to fill identified gaps. Also, participants will complete Values Clarification/Goal Setting Worksheets and craft a brief personal narrative that elaborates the rationale, values, and passion for their career path. Session 3 will focuses on improving goal setting skills using reflection on personal strengths and values, as well as effectively using peers and mentors to help design, implement, and track achievements and goals. Before the next session, mentees will revise the personal narrative and review it with their mentor. Session 4 will have participants apply a conceptual framework for making personal work choices that promotes academic growth and persistence. Time management strategies will be reviewed in the context of achieving work goals, and an interactive network exercise will be used to reinforce networking skills important in building professional relationships. Additionally, we will have an interactive presentation on writing effective letters of support.

Our Evaluation Core's evaluation demonstrates that CO-Mentor consistently achieves high levels of participant satisfaction from mentors and mentees during its first 5 years. As a result, 95% of mentees agreed/strongly agreed that they had greater clarity regarding their career path and development needs and 91% of mentees were more confident that they could successfully establish mutually-agreed upon goals and expectations with a mentor. Mentors reported the most significant gains in the following skills: providing coaching using generative questions (p=0.001), developing and reviewing a personal career development plan (p=0.002), identifying strengths and gaps in the mentoring team (p=0.004), and intentionally working to achieve a satisfactory work-life balance (p=0.001). Of the mentors, 26% were assistant professors, 45% were associate professors, and 29% were full professors. Of the mentees, 59% were assistant professors or instructors while 41% were MD fellows or PhD post-doctoral fellows. Thus CO-Mentor appears to reach its objectives and will be further enhanced in the next grant cycle as below.

***Further Development and Dissemination of CO-Mentor**:* Mentors can likely benefit from refreshing their mentoring skills and have called for booster sessions to be added. Based on this feedback from past participants, in the next grant cycle, we will develop mentorship consultations (one-on-one sessions for advice/guidance) and booster/refresher sessions to hone specific skills. Individual consultations can occur with a mentor or mentee only or as a mentor-mentee dyad and would last about 30-60 minutes. The focus of the consultation would depend on the reason(s) for the request and would involve identifying up to three most challenging aspects of their current mentor-mentee relationship(s) and identifying how to apply the concepts learned during CO-Mentor to optimize these relationships. Topics for booster sessions will include: 1) Aligning expectations, 2) Time management, 3) Cultural awareness, and 4) Conflict management techniques. Such initiatives will provide a mechanism to systematically explore/assess both facilitators and barriers to putting into practice the concepts, tools, and techniques introduced during the training – information that would advance our understanding of the environment for mentorship at CCTSI-affiliated institutions.

Our innovative CO-Mentor program has gained the attention of other CTSAs that desire implementing similar programs and thus dissemination will be a focus of activity. Dr. Austin has been collaborating with the University of Miami CTSA (See Letter of Support) and has traveled to meet with their CTSA and Career Development leadership to discuss piloting, testing, and implementing CO-Mentor. We plan to further disseminate the CO-Mentor curriculum to other CTSAs and to help those CTSAs implement the program successfully. The dissemination and implementation model will involve a combination of online materials and on-site instruction to apply learning. Dissemination and implementation will occur over 6 phases:

- Phase 1) From 2018-2019, develop a course tool kit that contains the necessary materials/resources to deliver the program, such as a curriculum manual, trainer's manual, slide decks, workbook, etc.;
- Phase 2) From 2018-2019, understand and address readiness for external CTSAs implementation by conducting a readiness survey for implementation and have future implementers complete the program;
- Phase 3) During 2019, provide train the trainer program to participating external CTSAs involved in piloting to build the necessary skills and to address readiness issues for implementation;
- Phase 4) From 2019-early 2021, pilot, evaluate and refine materials based on implementation experiences in piloting sites;
- Phase 5) In 2020, based on readiness work and pilot implementation experience, develop a dissemination plan for broader scalability; and
- Phase 6) Starting in 2021, disseminate CO-Mentor to interested national CTSA hubs and other academic health centers. For additional detail on the evaluative approach please see Section B.4 Program Evaluation below.

B. 3.3 Specific Aim 3: Support the future success of trainees through integration into the clinical and translational science community and disseminating scholarly products while building a scholarly portfolio.

B.3.3.1. Immersion with Translational Mentor*:* Given that TOTTS trainees are novice researchers and early in their careers it is essential that they begin to sense that they are part of the fabric of the CTR community. It is critical to have a socialization and acculturation experience that avails broadening ways of thinking. Therefore each trainee will have a translational mentor that will be a liaison to the community of the target audience apropriate to the trainee's area of research. For TOTTS trainees in a biomedical PhD program or part of the post-doctoral DVM track, having a clinical experience is crucial to understanding the context of human disease and illness and for developing interdisciplinary communication and team work. Each PhD biomedical and DVM

trainee will have a clinical mentor who works with the trainee to **develop a clinical experience relevant to the trainee**. Requirements for the clinical immersion experience include: 1) attending the clinical experience orientation, 2) shadowing their mentor in a patient care environment, understanding the patient's experience with their disease, and discussing medical problems of patients relevant to their research, and 3) maintaining a reflective diary with entries made on patients seen during each clinical attendance. The frequency of clinic attendance will be tailored to each individual project. On average, trainees will attend clinic with their clinical mentor for 8 hours per month. PhD students will report on their clinical experience at thesis committee meetings, and include a clinical experience chapter in their theses. Dr. Marion Sills will assist all biomedical and veterinary trainees and applicants to the program to identify a clinical mentor, if assistance is needed. TOTTS trainees in doctoral health professional degree or medical residency programs will identify a translational mentor and have the option of **developing an immersion experience in a biomedical lab or a health-oriented patient advocacy community relevant to the trainee**. Community liaisons from the Community Engagement Core will assist trainees in finding a translational mentor and a community immersion experience, if necessary, and will also provide an orientation for partnering and building relationships with commuity partners. Montelle Tamez of the CCTSI Community Engagement Core (**see Component C. Community and Collaboration**) will be the contact for trainees. Dr. John Tentler will assist trainees who desire a biomedical laboratory translational mentor and immersion experience. As described for clinical care immersion experiences, trainees will spend about 8 hrs/month and will be required to: 1) attend an orientation (lab safety for those doing a biomedical lab immersion and partnering and building relationships for those doing a community immersion experience), 2) shadow their mentor in a selected environment and discuss issues relevant to their research, and 3) maintain a reflective diary/journal with new entries made for each day.

B.3.3.2. Integration into the CTR Community for URM Trainees: For URM TOTTS trainees, they will have a mentor who is also a URM CTR investigator that they will meet with regularly (at least every 2 weeks) throughout the program. Four seminars for URM mentee-mentor dyads lead by Dr. Zimmer will be held to allow for discussion of challenges, obstacles and strategies for succeeding in research and academia. Topics will include: 1) Unconscious bias: participants will explore origins of biases, identify unconscious biases and practice strategies for addressing and mitigating the impact of unconscious biases. 2) Micro-aggressions: Different types of microaggressions (microassaults, microinsults and microinvaldiations) will be defined. Using their personal experiences and modified real-life cases, they will discuss approaches to microaggressions that occur in academia, the workplace and in our lives that impact relationships and team success. 3) Development and leadership of diverse teams: Participants will discuss team management strategies that focus articulating and demonstrating advantages of diversity for excellence in research teams. Discussion of personal strengths and weakness in communication and leadership will also occur. Additionally, all of these topics will be interwoven into TOTTS Seminars and CO-Mentor and LITeS for the broader CCTSI community.

B.3.3.3. Participation in the National CTSA Research Conference: A major career development focus of the program is preparing trainees for the National CTSA/ACTS Annual Translational Science Meeting. All trainees will be supported to attend the national conference. In preparation for their presentations, a TOTTS seminar will focus on Best Practices in Abstract, Oral, and Poster Research Presentations and will include a practice session that all trainees will participate in prior to conference attendance. Additionally, the national conference is an excellent networking opportunity outside of the CU and CSU systems for trainees.

B.3.3.4. Career Development Grant Review and Mock Study Section: Career Development (NIH "K") awards are an important means of providing research training and mentoring to junior investigators, thus facilitating their ability to successfully conduct independent research and compete for major grant support. TOTTS trainees, especially the post-doctoral fellows and PhD students in their final year, will be encouraged to participate in the CCTSI's Career Development Grant Review and Mock Study Section (Pre-K). The program's goal is to assist trainees (and their mentors) to write competitive career development awards by providing a local pre-review of applications. Mock grant reviews are conducted corresponding with NIH deadlines. Cara Wilson MD, a translational immunologist and HIV researcher, and Paul MacLean PhD (see Biosketches), a translational scientist who studies the metabolic consequences of obesity, direct the program. Drs. Wilson and MacLean work with a core team of reviewers to pair experienced senior reviewers with successful junior career development award recipient reviewers to provide internal expertise in writing mentor letters, candidate and career development plans, and specific aims. Grant applications are reviewed by 2-3 independent reviewers and scored using the NIH grant scoring system. In a study section manner, trainees will have the opportunity to hear how their grant scored with reviews followed by a question and answer period in which they may seek specific advice regarding how best to improve their applications. Written reviews are provided to all applicants. Preliminary

data indicate that the **Career Development Award Grant Review and Mock Study Section Program has an overall application success rate of 88%** compared to overall NIH success rates of 35-40%[44-45]. More than $12M in grant support has been awarded related to these grants. Based on participant feedback and our experiences we have identified areas for improvement for the next grant cycle: provide guidelines and supports/templates for preparing mentor's and institutional letters of support, increase the number of local reviewers with expertise in health services and health outcomes, and provide detailed biostatistical feedback when warranted. The Career Development Award program of the CCTSI is unique both in its approach by providing mentoring to both applicants as well as to junior reviewers. Through this process, both a sense of community with other researchers and a commitment to mentoring are built.

B.4. Program Evaluation

Goal: Enhance TOTTS capacity for team-based CTR across the pre-clinical to population health spectrum, leveraging our minority pipeline, to build a diverse workforce of clinical and translational researchers. Our Evaluation Core will lead TOTTS program evaluation and follow the logic-model provided below in **Table 9**.

Evaluation focuses on assessing TOTTS effectiveness to attract and support training and persistence of individuals from diverse backgrounds who have potential to infuse clinical translational research with new perspectives/insights and novel methods/approaches. Thus we will capture common metrics of CTR persistence and URM characteristics of TOTTS applicants, participants and alumni. Our conceptual Model for Persistence of a Diverse Clinical and Translational Research Workforce (See Figure 1 and Section A.3 above) guide the programmatic features of TOTTS and thus will be used to guide evaluation. Our conceptual model is a synopsis of theories and research regarding factors most predictive of engagement, achievement and persistence, with a specific emphasis placed on understanding experiences and outcomes for underrepresented minorities in CTR. As one example, our conceptual model features "goals thinking" and "pathways thinking" as central to the formation of a conceptual roadmap for a CTR career, which begins to be operationalized through the ICDP. The trainee's conceptual roadmap for delineating a concrete and intentional career path will be nurtured and honed through process of creating, reviewing, and revising ICDP, as self-reflection and with mentors. Skills to actualize plan will be developed and reinforced through tailored coursework, mentorship and coaching, CO-Mentor participation, and TOTTS Seminars. Evaluation, in turn, will triangulate program-monitoring data regarding progress and growth in relation to ICDPs, as well as facilitators and challenges. The extent to which trainees are able to describe alternative pathways to success when they encounter barriers will be an indicator of "agency thinking" – a factor also featured in our conceptual model as salient to enduring goal commitments. In addition, evaluation will be tailored to meet different stages of career development (pre and post doctoral).

Enhancing the CTR orientation of trainees' research is a key outcome. The Translational Orientation Assessment tool developed by the Evaluation Core will be used to compare the translational orientation of trainees' PhD dissertations and publications with those of their program peers. The assessment features 4 domains: (1) Translational Research Perspective, (2) Innovative Approach/Novel Applications, (3) Multi-Disciplinarity, and (4) Translational Implications. Each domain has three items. Reviewers assign a score of 1, if evidence of an item is demonstrated, and provide evidence as support; they score a 0, if no evidence of the item was found. Importantly, this tool will be helpful to program administration and mentors in determining the degree to which each trainee demonstrates key competencies and ways of thinking about his/her research (e.g., positioning their research within the context of the translational spectrum, demonstrates ability to anticipate how research findings may inform or advance research in other parts of the translational spectrum). Prior to using the tool, it will be validated through an external expert review process involving the following steps: (1) identify a group of CTR investigators representing the CTSA network who collectively bring expertise across the translational research spectrum; (2) conduct expert review and consensus building for items using the Delphi method; (3) refine; (4) pilot test, (5) refine as needed; (6) apply in local evaluative efforts, summarize results and share with the Leadership Advisory Council, CCTSI Executive Committee, CCTSI External Advisory Committee and in CCTSI's Annual Progress Report; and, (7) disseminate through publications and presentations and make it easily available to other TL1 programs and CTSA hubs.

Methodology: All trainees will be followed longitudinally for 10 years to document career trajectories that span TOTTS training to initial faculty appointments/career employment. Key informant interviews conducted at 1, 5 and 10 years post-program completion will explore how well the TOTTS program prepared trainees to navigate career transitions and achieve critical career milestones, as well as suggestions for improvements to optimize the preparation and success of future cohorts. In addition to primary source data collection (interviews, validated instruments and surveys), the Evaluation Core will use existing data sources, such as NIH Reporter and CU's

Office of Grants and Contracts, to track research productivity – specifically, grant success and overall funding levels. Trainees' demographics, additional CCTSI program participation and outcomes will be updated in an ongoing manner but no less than annually. Finally, any Common Metrics to be defined by the CTSA Consortium for evaluation of the TL1 Training Program will be collected and reported by our Evaluation Core.

Table 9: Logic Model for TOTTS Evaluation

Inputs	Output	Outcomes and Impact		
		Short (1-2yrs)	Medium (3-4 yrs)	Long (>5yrs)

• **CCTSI infrastructure and integrated network for training and promoting CTR across the translational spectrum**
• **Culture of team-oriented science**
• **Protected time**
• **Diverse network of translational, clinical, and research faculty for mentorship**
• **Diverse array of integrated education, training and career development offerings to extend pipeline, such as**
- **Coursework**
- **LITeS Jr.**
- **CO-Mentor**
	• Attract and retain diverse trainees
	• Rigorous training to build CTR competencies
	• Modeling and skill development for team-based CTR
	• Mentorship through multi-disciplinary teams
	• Exposure and experiences in CTR across the study lifespan and translational spectrum
	• Individualized career coaching, ICDP
	• Activities for CTR integration
	• Meaningful research and translational experiences
	• Create affinity groups: TOTTS seminars
	• Provide positive validating experiences
	• Address environmental pull factors
		• Increased diversity in applicant pool and funded trainees
		• Reduce environmental pull factors
		• CTR competencies
		  • Study design
		  • Research conduct
		  • Ethical and regulatory principles
		  • Dissemination (publishing and presenting to scholarly audiences)
		  • Grant writing
		• Identity formation as a CTR scientist
		• CTR community integration
		• Enhanced translational orientation
		• ↑Self- and coping efficacy
		• ↑Goals, pathways and agency thinking (from Hope theory)
		• Satisfaction with mentoring team and their mentorship skills
			• Institutional and CTR connectedness
			• Accelerated achievement of academic milestones
			• Production and dissemination of scholarly products
			• Positive stress management and coping
			• Persistence in CTR (continued training, career development award, employment)
				• Alumni actively engaged in team science
				• More diverse clinical and translational research workforce/teams
				• Infuse CTR with new perspectives, methodologies and technologies
				• Secure first Career Investigator Award
				• Persistence in CTR

B.5. Trainee Candidates

As a collective, we have a very large and diverse pool of qualified and eligible applicants from biomedical, medicine, social science, veterinary medicine and health disciplines (See **Table 10**) who would be ideal TOTTS candidates. **Program recruitment efforts** will be multi-faceted and include: 1) Emailing requests for applications to the entire CCTSI community, including affiliate hospitals, CU-D, CU-B and CSU at least 8 weeks before the deadline. 2) TOTTS program directors will attend annual student orientations for programs listed in **Table 10** and CSU CVMBS to promote the program and alert potential candidates of this unique training program and opportunity. 3) Directors of programs listed in **Table 10** and CSU CVMBS will be made aware of TOTTS and how to connect students with appropriate TOTTS program directors. Dr. Cicutto is a member of the CU-D Graduate Council and CU-D Graduate Program Directors Committee and will promote the program and alert directors to upcoming application deadlines. She will also work closely with CU-D Graduate Program Directors to identify URM trainees interested in CTR. 4) TOTTS will be prominently displayed on the CCTSI's and CU-D's websites. 5) Dr. Zimmer is instrumental in the SOM's training programs of medical students and residents. She will highlight the program at annual orientations for all medical students and residents to ensure that they are aware of the opportunity. Additionally, she attends a bi-monthly seminar/club for those interested in research careers, which attracts over 70 attendees that will be strongly encouraged and supported to apply. 6) TOTTS trainees will also be requested to serve as ambassadors by sharing their experiences and answering questions of peers in their home degree programs.

B.5.1. Applicant Pool

B.5.1.1. URM Trainees. Our target is 25-30% of TOTTS trainees will be underrepresented minorities and thus will help to address the disparity of URMs in CTR careers. Underrepresented populations for this application are consistent with NIH guidelines and include underrepresented racial and ethnic populations (Black or African

American, Hispanic, American Indian, Alaskan Native, Native Hawaiian, or Pacific Islander), individuals with disabilities, and individuals from disadvantaged backgrounds (NOT-OD 15-053). Refer to **Table 10** for the number of URM students based on race and ethnicity alone (not including disadvantaged background and disability) for potential TOTTS feeder programs. CU will be implementing an electronic record that captures disadvantaged background and disability of applicants starting in AY2017-2018. Dr. Zimmer organizes and holds SOM URM seminars held every 4-8 weeks for medical students and residents. She will ensure that URM medical students and residents are aware of TOTTS and, if interested, will be provided mentorship and support for completing the TOTTS application. For 2016-2017, there were 111 URM medical students and 100 URM residents eligible for TOTTS based on ethnicity, race, disability, and disadvantaged status. Dr. Martinez, Office of Inclusion and Outreach (OIO), organizes regularly held student life activities for URM students on both CU-D downtown and medical campuses. The OIO has worked diligently to develop and maintain relationships with URM students and to engage them with university life. As TOTTS and OIO goals are aligned, Dr. Martinez and his staff will ensure URM students are aware of and provided support in the application process. In 2016, there were 274 URM students, based on race/ethnicity alone, in the programs (excluding SOM) of students that the OIO are engaged with at least monthly. Both Drs. Zimmer and Martinez serve on the Leadership Advisory Council and a standing agenda item will be the recruitment and retention of URM trainees.

B.5.1.2. Doctoral Biomedical and Health Professional Students and Medical Residents interested in CTR from all of the CU-D doctoral programs outlined in **Table 10** will be eligible. Based on feedback from the CCTSI External Advisory Committee, medical students and residents will be directly targeted. For AY2016-2017, there were a total of 2,231 doctoral degree students of which 350 have ethnic and racial URM backgrounds. Also in AY2016-2017, there were 1,143 CU-D medical residents of which 8% are URMs. These data support the existence of a qualified applicant pool to select 11 highly qualified and motivated students for CTR and our TL1 program. It is anticipated that 1-2 trainees will be medical residents and 1-2 will be medical students for a maximum of 4 trainees per TOTTS training cycle with the remaining 7 slots being doctoral biomedical or health professional trainees. These data also suggest our ability to reach our goal of 30% of TOTTS trainees being from URM backgrounds. To be eligible, all applicants will have received a baccalaureate degree, be enrolled in and have completed the first year (as a minimum) of their doctoral program (PhD or professional doctorate). Medical residents will be eligible at any year of their residency training. As part of the application, the applicant will identify a research project mentor from his/her doctoral program. If the research mentor is not on the list of approved TOTTS mentors, program directors will review the proposed mentor's CV and past mentoring experience to ensure the mentor is highly qualified. If not highly qualified, a dual research mentor model will be suggested. Each trainee will also identify a translational mentor. For applicants needing assistance in identifying translational mentors, TOTTS directors will assist the applicant and research mentor.

B.5.1.3. Four DVM post-doctoral trainees will be recruited from CSU's CVMBS's pool of DVM prepared PhD students (n=12), post DVM trainees (n=32) and DVM residents (n=60), *providing a continuous pool of known and motivated DVM candidates to consider for TL1 research training*. Of this pool, 4-5 trainees/year are URMs.

B.5.2 Application and Selection Process. All applications will be submitted in early spring each year through the CCTSI's online submission portal with the majority of awards starting summer term. The application will include the applicant's CV, description of proposed research project and translational experience during TOTTS, statement of career goals including a future in CTR, letters of reference from research and translational mentors and one other person of their choice, a letter confirming good standing in program (not on academic probation, enrollment, etc.) and NIH biosketches for research mentors. Three members of the Recruitment and Selections Committee will independently review each application and top candidates will be interviewed. Holistic review of applications will include 50% of the weight allotted to the planned research project, translational experience, and career goals and 50% to experiences and attributes identified through the personal statement and letters of reference. In ranking applicants, a key consideration is whether TOTTS will significantly enhance their current degree program experience and their plan for pursuing a team-oriented CTR career CTR, which should be detailed in their personal statement. *Special attention will be paid to the diversity of the trainee group in terms of gender, minority, disability and disadvantaged status, and broad representation of doctoral degree programs, including interest and focus on health disparities and equity research.* Based on interviews and information contained in the application, the committee will arrive at a ranking for TOTTS slots, which will be shared, discussed and approval sought by the Leadership Advisory Council.

Table 10: 2016 Doctoral Program Enrollment of URMs (ethnicity and race) and Non-URM Students

Program/Primary Major	Non URM	URM	Total
Health & Behavioral Sciences	18	4	21
Integrative & Systems Biology	11	1	12
Clinical Health Psychology	24	3	26
School of Dental Medicine	338	59	397
School Psychology	37	11	48
Bioengineering	21	4	25
Biomedical Basic Science	10	1	11
Cancer Biology	27	8	35
Clinical Science	38	5	43
Computational Bioscience	14	2	16
Cell Biology, Stem Cells	25	4	29
Human Genetics & Genomics	12	3	15
Immunology	34	6	39
Integrated Physiology	6	2	8
Medicine	618	76	694
Microbiology	16	2	18
Molecular Biology	34	6	40
Neuroscience	26	4	29
Pharmacology	18	4	22
Physical Therapy	187	13	200
Rehabilitation Science	7		7
Structural Bio & Biochemistry	12	1	13
Nursing (DNP)	55	9	64
Nursing (PhD)	34	4	38
Pharmacy	526	83	609
Pharmaceutical Sciences	19	2	21
Toxicology	16	5	21
Biostatistics	9		9
Public Health	18	2	20
Epidemiology	16	3	19
Grand Total	**2231**	**350**	**2871**

B. 6. Institutional Environment and Commitment

The CCTSI, as a collective community of academic hospitals, universities, community partners, and their faculty and staff, are deeply committed to rigorous training and the development of TL1 trainees and outstanding investigative teams. Described below are their commitments and substantial supports to TOTTS.

- Participating institutions will assure that TOTTS directors and Faculty Mentors will be provided sufficient time to contribute to the proposed training and oversight activities.
- TOTTS mentors will participate with their TOTTS mentees in the CO-Mentor program (see B.3.2 above). Commitment for this activity includes faculty effort in the seminars and CCTSI support for offering CO-Mentor at no cost to participants.
- TOTTS trainees will be provided office and related research space, supplies, etc. by their faculty mentors and provided other infrastructural supports, such as administrative assistance, computer, internet, IRB, and IACUC, by CU-D, CU-B, CSU or participating hospitals.
- CCTSI offsets the cost of TOTTS trainee research by offering free or subsidized biostatistical support.

TOTTS is a distinct and necessary TL1 training program. As described above in Section A.2 Need for TOTTS, numerous reasons exist for the program. While there are several successful training opportunities available none of them prepare the future CTR investigator workforce in an interdisciplinary team-oriented manner across the translational spectrum. CSU's CVMBS has one T32 and it is substantially different from the proposed 1-year TOTTS program in that it provides 3 years of support for post-residency DVMs pursuing a PhD degree in a basic science field. In addition, our TOTTS program is uniquely modeled for achieving academic and CTR persistence with tailored supports for URMs, which also sets it apart from other programs that focus on training within a specialty area. (Section C below and B3.3.2 describe efforts to recruit and retain URMs.) Our program will be a catalyst and role model for other pre- and post-doctoral training programs on campus. Through discussions with CU-D (AMC) graduate program directors in preparation for this grant, it became apparent that a seed had been planted as other programs are now considering offering their trainees workshops to build leadership and team skills, as we have built into this proposal. To synergize efforts, we will organize some of the TOTTS Seminars on team science and leadership (LITeS jr. and SciTS Section B3.2.1a) to be open to other doctoral students. TOTTS is unique compared to other programs that receive external funding in that it prepares the next generation of CTR investigators to be fluent in team-based science while appreciating the full translational spectrum in contrast to programs that focus on excellence in niche or focused specialty research disciplines.

Our CCTSI and partnering organizations have numerous institutional strengths for our TL1 program. 1) Our partnership with CSU's College of Veterinary Medicine offers distinct and unique opportunities that will be capitalized. Our productive partnership allows us to address the need for greater numbers of veterinarians trained in translational biomedical research[1-4]—with expertise in comparative translational medicine to accelerate bench to bedside discoveries in a team-oriented manner. 2) Spero Manson, PhD (Pembina Chippewa), a medical anthropologist and Professor of Psychiatry, heads the American Indian and Alaskan Native Programs at CU-D.

His training programs (undergraduate, graduate and post-doctoral) include 102 Native communities spanning rural, reservation, and urban settings. His involvement in CCTSI training programs is an asset setting-us apart from other CTSAs and will be leveraged to increase the number of Native American trainees. 3) The CCTSI's Community Engagement Research Core is a leader and innovator in the field of community engaged research. They have developed several programs and resources that will be integrated into the TOTTS training program, including workshops on partnering with community, principles and practices for community engaged research, dissemination beyond the publishable paper, and consults with community liaisons and support in identifying trainee-community partners with similar interests. 4) Finally, we have two very strong offices at the University, SOM's Office of Diversity and Inclusion and CU-D's Office of Inclusion and Outreach, with a shared mission of instilling diversity into the institutional consciousness and accelerating research excellence through diversity. Their coordinated efforts to achieve this mission will be integrated seamlessly into the activities of TOTTS, facilitated by our monthly Leadership Council meetings.

New faculty recruited to CU-D and CSU with expertise in diversity of trainees, faculty and research teams will propel and synergize our efforts in attracting, retaining and building diverse teams, both from a demographic and discipline perspective. Both TL1 URM leaders, Drs. Shanta Zimmer (CU-D) and Gilbert John (CSU) were recently recruited from the University of Pittsburgh and Oklahoma State University, respectively, to enhance and expand efforts to recruit and retain URM students, trainees and faculty. We will leverage Dr. John's 20 plus years of experience and success improving the disparity noted with Native Americans in the biomedical and clinical sciences. Because of Dr. Zimmer's success in increasing diversity and inclusion at the University of Pittsburgh's internal medicine residency program and their CTSA training programs, she was recruited to Colorado to enhance workforce diversity. She will be working with TOTTS and other CCTSI programs to increase our URM diversity of trainees and support creating a culture of accelerating CTR excellence through diversity. Both of these faculty members will bring needed insight and expertise.

C. RECRUITMENT AND RETENTION PLAN TO ENHANCE DIVERSITY

To support the CCTSI's priority of attracting diverse trainees, the CU-D Office of Inclusion & Outreach (OIO) is expanding educational opportunities for URM high school and undergraduate students and will strengthen the URM pipeline into our TOTTS program. The OIO mission is to "instill diversity into the institutional consciousness; reinforcing equity and inclusion through policies, practices and programs that prepare all faculty, students and staff for a multicultural world". To strengthen recruitment of URMs and broaden the diversity of faculty, trainees and students, the OIO is implementing a comprehensive plan to: 1) Promote the academic advancement and success of URMs, 2) Enhance cultural, bilingual and diversity instruction throughout the curriculum, 3) Encourage an institutional climate of inclusiveness, respect and understanding, and 4) Promote innovative research and scholarship related to cultural and racial disparities in health and health care. To support recruitment and persistence of URM trainees, the OIO will be expanding educational opportunities along the educational pipeline. The primary goal of the URM pipeline of programs is to expose promising URM high school and undergraduate students to careers in CTR and to facilitate the transition of students in pipeline programs into our TOTTS and graduate school programs. The URM pipeline of partners, termed SUMMiT (Summer Undergraduate Minority Mentoring in Translational Science; See **Table 11** below**),** includes programs at Dine College (Navajo tribal college, Spero Manson), CU-AMC, CU-Denver, and CU-B. Consistent with our conceptual model of persistence (described above, Section A.3), these pipeline programs integrate students into the academic and social realms of our university and provide meaningful research experiences thereby strengthening their academic persistence, commitment to graduation, and interest in CTR[18]. *We anticipate a higher percentage of URMs in future years as our URM Pipeline Programs mature in attracting exemplary URM students to clinical and translational science*.

Efforts to improve diversity of the university and SOM are successful. Data suggests that enrollment of URMs has more than tripled, based on race and ethnicity, over the past 10 years in the SOM Residency Program. In 2007, the proportion of URM trainees was 3% and in 2013 it doubled to 6% and for 2017-2018 it will be 10%. Medical student URM diversity is 30% and has been 25%-30% for the last 4 years. These data demonstrate sustained and growing ability to attract URM trainees. Efforts to attract additional URMs for this next funding period will include: 1) The President of CU committing funds for URM scholarships, including those with disabilities or disadvantaged backgrounds. It is anticipated that 50% will receive some type of financial support. 2) Dr. Zimmer will provide training to program directors and staff in unconscious bias, diversity and holistic application reviews. 3) The SOM will host a "second look" event each year requesting URMs return to campus for another visit that will include a Dean's s reception with campus leaders and meetings with URM residents.

Table 11: Summer Undergraduate Internship Programs	Campus	Sponsored/Funding
Graduate Experience for Multicultural Students	CU AMC	NHLBI
Summer Undergraduate Research-Pharmacology	CU AMC	American Society for Pharmacology
Building Research Achievement in Neuroscience (BRAiN)	CU AMC	NIH R25NS080685
Undergraduate Pre-Health Program	CU AMC	OIO and Kaiser Permanente
Undergraduate Research Opportunity Program (UROP)	CU Denver/CU Boulder	Campus Funding
Maximizing Access to Research Careers – Undergraduate Student Training in Academic Research (MARC U-STAR)	CU Denver	National Institute of General Medical Sciences (T34 GM096958)
Child Health Research Internship	Colorado Children's Hospital	Department Funding
Summer Research Enhancement Program (SREP)	Dine College	NIH (5P20MD006872) & NIH (2P60MD000507)
BSI Scholars in STEM Undergraduate Research	CU Boulder/CU AMC	Howard Hughes Medical Institute (HHMI)
Summer Undergraduate Research Fellowship (SURF)	CU AMC	American Society for Pharmacology and Experimental Therapeutics
Pediatric Mental Health Institute	Colorado Children's Hospital	Department Funding
Cancer Research Fellowship Program	CU AMC	NCI
Veterinary Summer Scholars Program	CSU	NIH/industry/foundational

CCTSI TOTTS Program Expansion To Support Diversity

Diversity as a means for accelerating research excellence (DARE) will be woven throughout TOTTS as a means to improve recruitment and retention of URM trainees. As described above, recruitment efforts will be in partnership with the SOM Office of Diversity and Inclusion (ODI) and the CU-D Office of Inclusion and Outreach (OIO) who apply best practices for enhancing the applicant pool. TOTTS Recruitment and Selections Committee members will attend a workshop provided by Drs. Zimmer (ODI) and Martinez (OIO) on following a holistic applicant review processes with specific attention given to diversity in the selection process. To support retention and integration, TOTTS URM applicants will be given additional mentorship support through their assigned URM mentor (Zimmer and John; Section B.1.1) and will attend four seminars dedicated to discussing progress, challenges and strategies for succeeding in CTR (Section 3.3.2). To support a broader culture for diversity accelerating research excellence across the CCTSI, training sessions on unconscious bias, microaggressions and diversity in teams will be added and interwoven into CO-Mentor and LITeS programs.

COMPONENT J: NRSA TRAINING CORE (TL1 PROGRAM)

PLAN FOR THE INSTRUCTION IN THE RESPONSIBLE CONDUCT OF RESEARCH

Training in the ethical and regulatory principles, including Responsible Conduct of Research (RCR) and Good Clinical Practice (GCP), is critical to the efficient conduct of clinical-translational research (CTR) and maintaining societal trust in the research enterprise and thus is an essential part of the education and training TL1 Training Program at the Colorado Clinical and Translational Sciences Institute (CCTSI). The University of Colorado Denver (CU-D) and the CCTSI believe that RCR training is an essential educational component for trainees pursuing CTR careers. Because RCR is most effective in the scope of daily activities, the plan for RCR training will be tailored to meet the specific needs of the individual trainee. However, all CCTSI TL1 trainees will complete a responsible conduct of research and ethics course that includes Good Clinical Practice, which will be an identified milestone and review criterion of their ICDP. The CCTSI and the University will provide several RCR educational opportunities to TL1 trainees, their mentors and collaborating faculty and staff. Educational opportunities are designed to be in full compliance with the policy requirements for RCR education promulgated by NIH in NOT-OD-10-019.

A. Format

The CCTSI infrastructure provides multiple modalities and initiatives to ensure that all TL1 trainees are prepared to conduct efficient, safe, best practice oriented translational research. Modalities of instruction provided will include: 1) formal graduate level courses (CU-D: CLSC 7150, CLSC 7151, CLSC 6590, BIOS/PHCL 7605, IDPT 8890; CSU BMS 610, PHIL/CM666, Grad 544, MIP 654) involving lectures, face-to-face discussion, and application of content that follow NIH recommended curricular requirements (NOT-OD-10-019), 2) lunch hour workshops offered through the Regulatory Knowledge and Support (RKS) Core, 3) short courses offered through the RKS Core, 4) ethics conferences and guest lectures, and 5) online modules for self-paced instruction. **All TL1 trainees will complete a formal research ethics and responsible conduct course that entails over 15 hours of face-to-face instruction, dialogue, application PLUS completion of CITI modules (HIPAA, GCP, human subject protection, and RCR).**

***A.1.Basic training*.** All TL1 trainees will be required to complete Collaborative Institutional Training Initiative (CITI) online modules for Basic Course in the Protection of Human Research Subjects, the CITI HIPAA Course, CITI Responsible Conduct of Research and the CITI Good Clinical Practice module and if appropriate, completed the required CITI refresher courses on an every three-year basis. Trainees that have not already completed CITI modules and an approved graduate course in their doctoral program before starting the TL1 program, will complete the CITI modules AND a 4 hour face-to-face *Getting Started in Research Workshop* offered by CCTSI's Regulatory and Knowledge Service Core on the last Wednesday of July before they receive TL1 funding.

A.2. Advanced Training. All TL1 trainees will be required to complete an Ethics and Responsible Conduct of Research course that follows NIH recommended curricular requirements (NOT-OD-10-019). TL1 trainees will complete an Ethics and Responsible Conduct of Research course either through the Clinical Science (CLSC) Graduate Program for CU-D students or the BioMedical Science (BMS) Program's course for Colorado State University's veterinary trainees. It is anticipated that some of the TL1 trainees will have completed a comparable graduate course as part of their doctoral program before starting the TL1 program and as long as the course meets the NIH recommended curricular requirements (NOT-OD-10-019), they will not be required to complete one of these courses during their 1 year of TL1 training. Trainees with health care provider backgrounds will also be required to complete the CLSC course, *Conducting Clinical Trials for Investigators*. Topics covered in this course will include GCP, common deficits in clinical trials, grant management, data management, preparing for audits, and regulations surrounding studies evaluating devices and therapeutics (drugs). All of these courses include the application of learning through assignments that are relevant to current research endeavors. An assignment example is to identify the process of setting up a mock clinical trial including identifying budget items, thinking about staff needed, writing a subject management protocol, planning recruitment strategies and characterizing informed consent process. In addition, RCR, GCP, and associated topics will be integrated into the bi-monthly TL1 trainee seminars. Trainees will also be strongly encouraged to

attend other educational opportunities offered through the Regulatory and Knowledge Core, such as lunch hour workshops, short-courses, ethics conferences, or individual consults.

B. Subject Matter

Topics covered in required coursework and educational opportunities will include: ethics and regulation of human subject protection, preparation of a consent form, human embryonic stem cell research, industry-sponsored research, confidentiality, respect, identifying legal and regulatory constraints, scientific integrity, ethical theories and principles, live vertebrate animal subjects in research, federal and institutional guidelines for research pertaining to human and animal models, safe laboratory practices, data acquisition, management, ownership and sharing, mentor/mentee responsibilities and relationships, collaborative research including collaborations with industry, conflicts of interest, peer review, and responsible authorship and publication. Online CITI training in Responsible Conduct of Research offers modules by discipline type: biomedical, social and behavioral sciences, physical sciences and humanities.

C. Faculty Participation

Research mentors will be required to demonstrate completion of training for RCR and GCP within the last 3 years. A requirement of all personnel involved in any clinical-translational research throughout our institutions is the completion of CITI online training modules for HIPAA, GCP, human subject protection, and RCR in addition to attending face-to-face workshops of no less than 8 hours occurring no less than every 3 years. All University of Colorado Denver faculty/staff are able to take any of these courses at no cost through their University tuition reimbursement program.

TL1 Program faculty/mentors will meet at least weekly with TL1 trainees and oversee progress according to the trainee's Individual Career Development Plan (ICDP) for research, training, career development, including completion of ethics, GCP and RCR training. Research mentors will be responsible for ensuring that the trainee adheres to ethical and regulatory practices (including RCR and GCP training, IRB and IACUC approvals, when appropriate), maintains research-training certificates and documents on the ICDP. TL1 Program faculty will be involved in both formal and informal instruction related to RCR and GCP. Information exchange will occurs in the course of laboratory interactions, clinical experiences, and other research related situations and more formally as discussion leaders, speakers, and lecturers.

In addition to TL1 faculty/mentors, Dr. Marilyn Coors, (Regulatory Core), Dr. Allan Prochazka (CLSC program) and Dr. Barbara Hammack (Regulatory Core and CLSC) are instrumental in educational opportunities and courses. **Allan Prochazka MD, MSc** is the past chair of CU-D's IRB and has performed research on informed consent, including a randomized trial of repeat back to enhance surgical informed consent. Since 1999 he has taught responsible conduct of research and research ethics graduate classes for the Clinical Science Program. **Barbara Hammack PhD** is the Manger of Research Services for the CCTSI and the University and has expertise in protocol development. She will be a tremendous asset for junior investigators starting to develop necessary skills for success in CTR. She teaches the CLSC course, *Conducting Clinical Trials for Investigators.* **Marilyn E. Coors PhD** is Associate Professor of Bioethics at the Center for Bioethics and Humanities and Director of Research Ethics for the CCTSI. She holds a Ph.D. in bioethics, and the ethical issues in clinical genetics and genetic research are the foci of her research, teaching and professional service. She will provide cross-disciplinary ethics education through the TL1 Trainee seminars and ethics conferences held throughout the year and provide individual research ethics consultations.

D. Duration of Instruction

All TL1 trainees will complete a formal research ethics and responsible conduct course that entails over 15 hours of face-to-face instruction, dialogue, application PLUS completion of CITI modules (HIPAA, GCP, human subject protection, and RCR). Courses are offered every year during spring and fall terms and have been specifically designed and designated by the University of Colorado Denver to meet all NIH guidelines requirements. In addition, another 10 hours of discussion and instruction will occur through the TL1 Trainee Seminars. Clinician trainees will also be required to complete a 23-hour contact hour course, *Conducting Clinical Trials for Investigators,* during the TL1 Training Program. See the Format section above for additional detail.

E. Frequency of Instruction

Frequency and type of instruction depends on the individual trainee but all trainees will complete RCR, GCP and ethics training. As most trainees will start the CCTSI TL1 Training Program in July, in the middle of a summer term, trainees will be required to register and attend the 4-hour, face-to-face Getting Started in Research Workshop offered by CCTSI's Regulatory and Knowledge Service Core provided in July unless they have already completed a graduate level course in ethics and RCR along with the CITI modules (HIPAA, GCP, human subject protection, and RCR). In addition, trainees will subsequently be required to demonstrate fall term enrollment in an ethical and responsible conduct of research course in the Clinical Science (CLSC) Graduate Program for CU-D students or the BioMedical Science (BMS) Program's course for Colorado State University's veterinary trainees term and then in January submit proof of course completion with a minimum grade of a "B" otherwise TL1 funding disbursement will not occur for the trainee. If the trainee had already completed the RCR and ethics course plus CITI modules, this must have occurred within 20 months of starting the one-year long TL1 training program otherwise the CLSC or BMS course will be completed during training. Additionally, at least 10 hours of content and discussion will occur over the year long TL1 Trainee Seminars. Clinician trainees will also be required to complete a 23-hour contact hour course, *Conducting Clinical Trials for Investigators,* during the TL1 Training Program.

F. Compliance

TL1 funding will not be provided to trainees until proof of completion or enrollment is provided to the TL1 Program Director and Program Administrator. Research mentors will also be required to demonstrate completion of training for RCR and GCP within the last 3 years. In addition to the documentation required by trainees and their mentors, the Colorado Multiple Institutional Review Board requires proof that all trainees and personnel involved in research have successfully completed the Collaborative Institutional Training Initiative (CITI) Basic Course in the Protection of Human Research Subjects, the CITI HIPAA Course, CITI Responsible Conduct of Research, and the CITI Good Clinical Practice module and have required completed CITI refresher courses on an every three year basis.

As detailed in components E-Research Methods and G-Network Capacity, CU-D in collaboration with UCHealth and Children's Hospital Colorado, will transition the current pre-review and management of study protocols into OnCore (a CTMS) to further streamline processes. We will use the centralized database provided by OnCore to track mandatory training listed above, licensing of and credentialing of research personnel. Members of the research team will only be granted access to OnCore upon completion of the requisite GCP and RCR training. Through these courses and Oncore, standard operating procedures, template forms and checklists will be made available for research teams that can be adapted to meet their needs. Site initiation visits and periodic audits by the Regulatory Core will trainees and their mentors in meeting regulatory standards when operationalizing their protocols.

G. Review and Quality Improvement

Every year the Translational Workforce Development, TL1 Training Program, and Regulatory Cores will review participant evaluations and discuss strengths and limitations of current offerings to identify the need for and types of revisions necessary. For the last 8 years the CLSC Ethics and Responsible Conduct of Research Course receives very high marks (scores over 4.5 on a 5 point scale) in terms of relevance, stimulation of critical thinking, application, and knowledge of the professor/instructor. Every year Dr. Prochazka, the course professor, is nominated for Best Teacher of the Year Award within the CLSC. The CCTSI is strongly committed to upholding the highest ethical, regulatory and professional standards in research endeavors and ensures that anyone involved in clinical and translational research are trained and remain current in best practices.

COMPONENT J: NRSA TRAINING CORE (TL1 PROGRAM)

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OVERALL: FACILITIES AND OTHER RESOURCES

UNIVERSITY OF COLORADO DENVER (CU-D) ANSCHUTZ MEDICAL CAMPUS

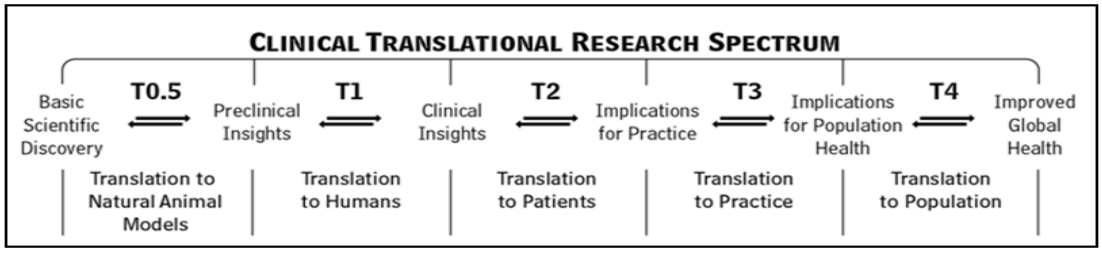
The UCD Anschutz Medical Campus (AMC) is the largest academic health center in the Rocky Mountain region which brings together on the same campus for the first time three hospitals and educational, administrative, and research facilities for all six health science schools of **CU-D**. The 11.3 million ft^2 of state-of-the-art facilities has benefited from over $4 billion of investments to date. The 230 acre campus provides adjacencies of clinical, educational, and research facilities all within walking distance of each other, building a new culture of collaboration among clinicians, investigators, and educators that invigorates research and innovation. An adjacent biotechnology park helps facilitate close collaboration between University investigators, industry, and the private sector.

COLORADO CLINICAL AND TRANSLATIONAL SCIENCES INSTITUTE

The Colorado Clinical and Translational Sciences Institute (CCTSI) was established in 2008 with funding from the Clinical and Translational Science Award (CTSA) initiative of the National Institutes of Health (NIH) and substantial support from the involved institutions. It is a collaborative organization which aims to transform existing clinical and translational research and training efforts into a shared research enterprise. The **Vision of the CCTSI** is to accelerate and catalyze the translation of innovative science into improved health and patient care. To achieve this vision, the **Mission of the CCTSI** is to:

- Catalyze and enhance scientific discovery, innovation, dissemination and translation across the lifespan
- Educate and sustain a resilient, innovative and diverse translational science workforce
- Promote and ensure an efficient, safe, collaborative and integrated research environment
- Engage stakeholders and communities across the entire translational spectrum (T05. to T4; Figure 1).

Figure 1. Spectrum of Clinical and Translational research



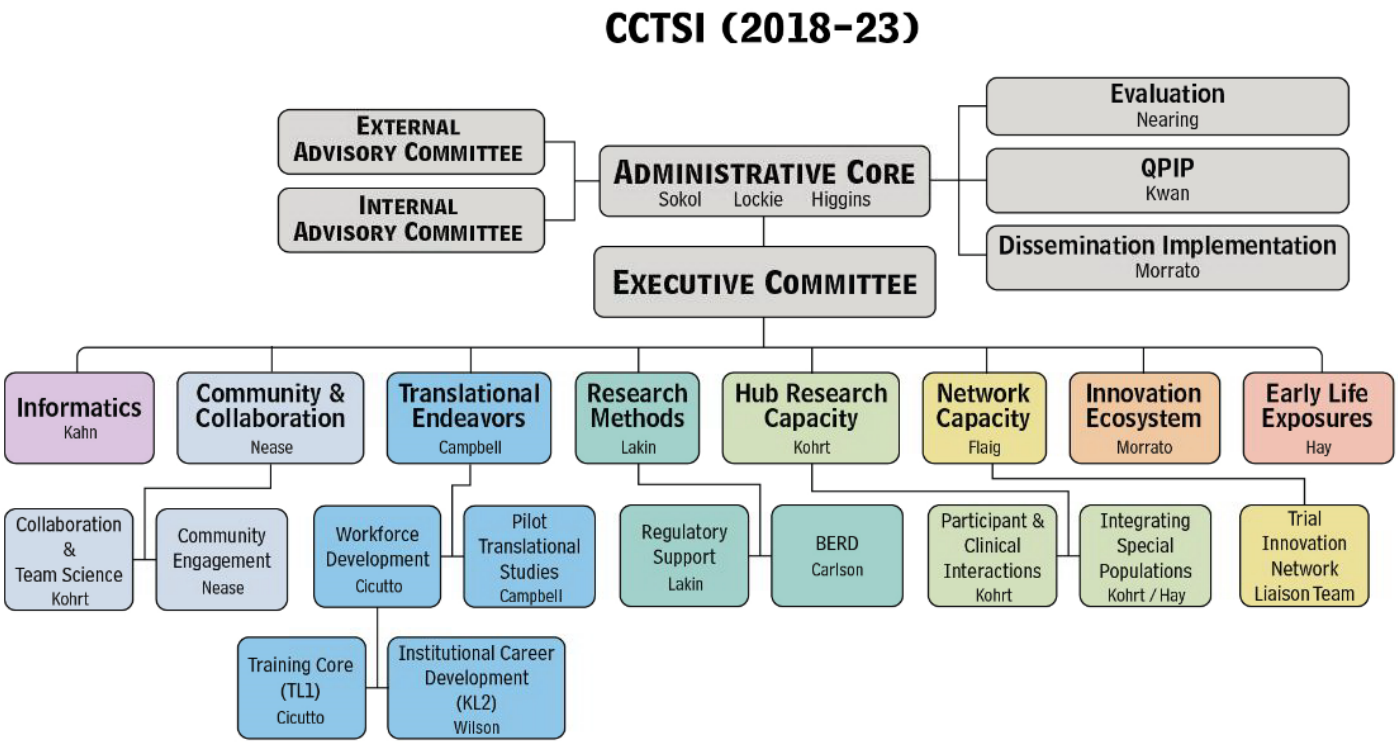
The CCTSI is an Institute within the University of Colorado, based at University of Colorado Denver Anschutz Medical Campus (CU-AMC). As such, CCTSI Program Directors and staff are generally housed within their home department, according to faculty affiliation. The Institute's resources, therefore, are distributed across the schools, campuses, and affiliated hospital that is serves. These include 5 Clinical Translational Research Centers (CTRCs) providing inpatient and outpatient clinical research resources at University of Colorado Hospital (UCH), Children's Hospital Colorado (CHCO), National Jewish Health (NJH), and CU-Boulder with an additional mobile perinatal CTRC; contact points at each hospital; and programs located across the AMC, downtown campus, our affiliated institutions across Colorado, and the hospitals. The CCTSI provides office space for administrative staff in the Leprino Office Building, located between the University of Colorado Hospital and the University of Colorado Denver. This space also houses conference rooms and open workspaces that allow CCTSI Program Directors and staff to collaborate and work together.

An Executive Committee, chaired by the CCTSI Director and Principal Investigator, Ronald J. Sokol, MD, oversees operations and decision making. Dr. Sokol reports to the Vice Chancellors for Research and the Vice Chancellor for Health Affairs (the Dean of the School of Medicine) of CU-D, who in turn report to the Chancellor of CU-D. The CCTSI involves the 6 health professional schools and colleges located at the CU-D AMC; the Schools of Engineering and Applied Science, Liberal Arts and Science, and Education and Human Development of CU-D Downtown Campus; the Colleges of Arts and Sciences and of Engineering and Applied Science at University of Colorado, Boulder; and the colleges of Veterinary Medicine and Biomedical Sciences, Liberal Arts, Health and Human Services, and Engineering at Colorado State University. Affiliated institutions include 6 local hospitals and health care organizations: University of Colorado Hospital (UCH), Children's Hospital Colorado

(CHCO), Denver Health (DH), National Jewish Health (NJH), Denver Veterans Affairs Medical Center (DVAMC), and Kaiser Permanente of Colorado (KP). Faculty, trainees, and research staff at each of these institutions may become CCTSI members to access CCTSI resources. Through the CCTSI's Partnership of Academicians and Communities for Translation (PACT), our community engagement and research program, it has 18 established Community-Academic partnerships throughout Colorado, involving diverse and underserved populations throughout the state. This collaborative network of universities, hospitals, and the communities they serve have successfully promoted excellence in health care professional training and cutting-edge research programs and innovation for the past 30 years. Investigators from all areas of biomedical, biobehavioral and health services research use the CCTSI to access resources for innovative interdisciplinary research and clinical and translational sciences training. The CCTSI requires membership of faculty, research associates and post-Docs, trainees, community members, private companies, and public entities in order to use CCTSI resources, training programs or facilities. In April 2017, we had 4,200 members.

The CCTSI organization structure has been re-engineered to align with the requirements of PAR 15-304. This is more fully discussed in the section of the grant A. Administrative Core.

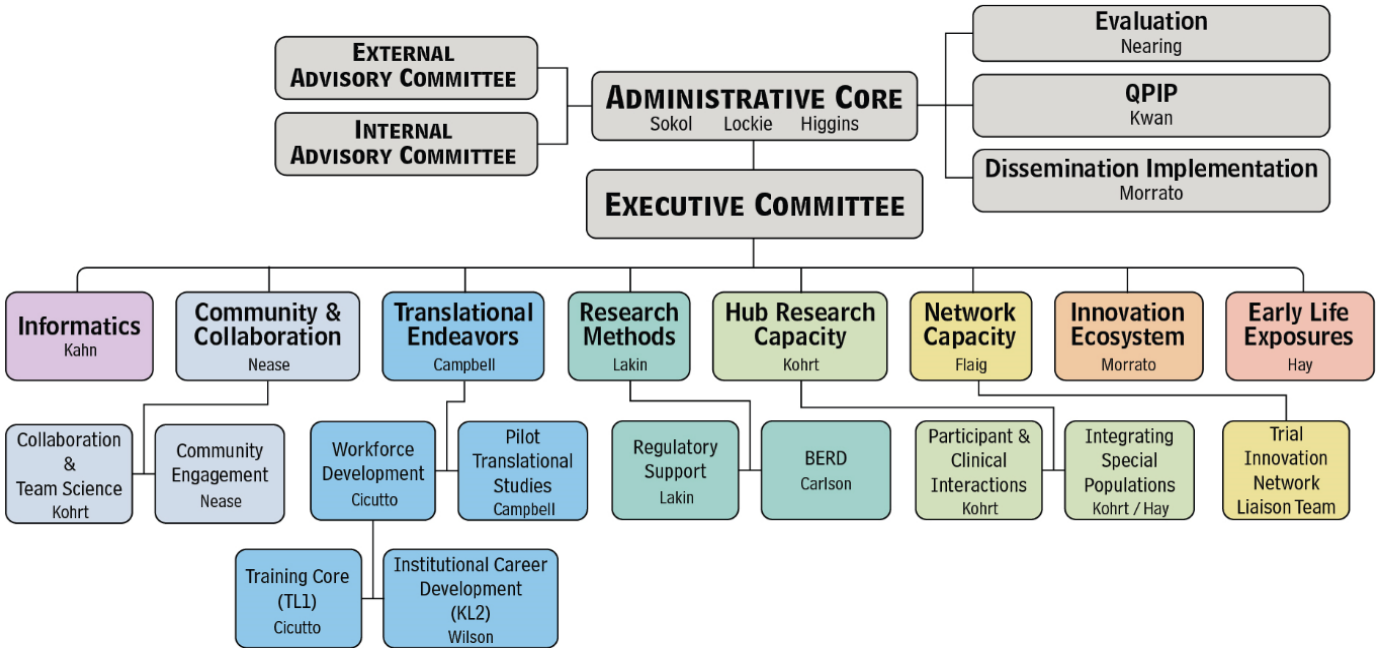
Overall Organization and Governance



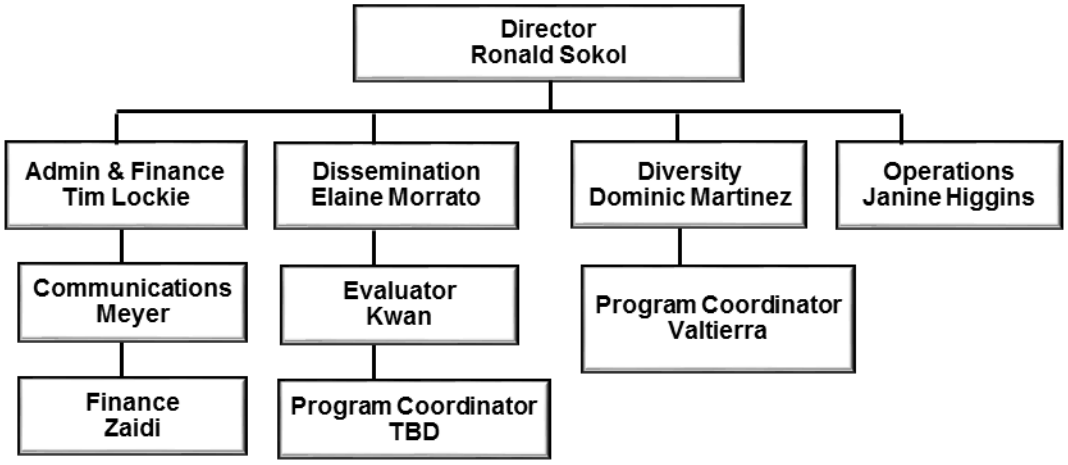
FACILITIES AND OTHER RESOURCES

A. ADMINISTRATIVE CORE

Organizational Structure of CCTSI



Administrative Core Organizational Chart



1. PARTICIPATING INSTITUTIONS

The CCTSI, based on the Anschutz Medical Center (AMC) of CU-D, will be the academic home for clinical and translational investigators and sciences at the 4 largest Colorado public research university campuses (AMC, CU-D Downtown, CU-B, & CSU), 6 academic hospitals and health care organizations, and over 20 community organizations and PBRNs located throughout Colorado (**Figure below**). The academic institutions and hospitals are located between Downtown Denver and Aurora, with the exception of CU-B (25 minutes away) and CSU (60 minutes away). These Colorado institutions

and communities have collaboratively achieved success over the past 35 years in promoting excellence in education and training in all health care professional fields and in cutting-edge research programs. The first 9 years of the CCTSI program transformed and solidified the academic and training relationships among these institutions. With this new CTSA grant application, the CCTSI will further re-engineer its structure and fuctions to align with the mission of NCATS and the national CTSA consortium, as outlined in PAR-15-304. ***The following describes the Anschutz Medical Center (AMC) and each partner institution and its important role in the CCTSI.***

The AMC vision. In 1995 the University of Colorado acquired 227 acres of the then newly closed Fitzsimons Army Hospital Base in the east Denver suburb of Aurora, with the plan to relocate and rebuild the overcrowded CU-D Health Sciences Center campus over the next 30-40 years. In response to unprecedented growth in research funding, and through a variety of public and private funding mechanisms, this rebuild was swiftly completed with relocation completed in 2008. The resulting AMC (**Fig. 1**) has geographically brought together for the first time the three major CU-D teaching hospitals and new educational, administrative and research facilities for all six health science professional schools. Soon to total over 1100 combined inpatient beds at AMC, the University of Colorado Hospital (UCH), Children's Hospital Colorado (CHCO) and the Denver Veteran Affairs Medical Center (DVAMC; to be completed in 2018) are located adjacent to each other (**Fig. 1**) and within easy walking distance of the education and research facilities. The 6.5 million ft^2 of new facilities will ultimately attract more than $4 billion in facility-related investments. The AMC is the largest academic health center between Chicago, Texas and the West Coast, with education, research and patient care facilities some of the best in the nation today. Available research space will eventually total 3.4 million ft^2, which is further enhanced by the adjacent 160 acre Colorado Bioscience Park Aurora, in which industry partners and faculty start-up companies are flourishing.

Figure 1. Location of CCTSI partner institutions and AMC

CU-D AND PARTNER RESEARCH UNIVERSITIES

- **UNIVERSITY OF COLORADO DENVER (CU-D)** is a comprehensive University within the region's largest metropolitan area, with a Downtown Denver Campus and the Anschutz Medical Center Campus nine miles east in Aurora, CO. With more than 27,000 students and 100 degree programs in 12 schools and colleges, CU-D awards more than 3,400 degrees each year and more graduate degrees than any other institution in Colorado. The **Downtown Denver Campus** is the most ethnically diverse college campus in Colorado, providing opportunities for improving minority and underserved population participation in training. **AMC,** the only Academic Health Center within the state of Colorado, is the central location of the CCTSI and is home to the 6 health profession schools. CU-D research and training *grant awards exceeded $437 million in FY 2016 with $206 million received from NIH*. *The Chancellor of CU-D and the Deans of each CU Health Profession School have provided Letters of Support.*

The AMC is home to the **CU School of Medicine (SOM)**, one of the outstanding public medical schools and research institutions in the United States. SOM houses the NIH-funded CU Comprehensive Cancer Center,

a working partner of the CCTSI with many shared programs. Over 60 SOM multi-disciplinary and interdisciplinary research centers, institutes and biotechnology core facilities form the nexus for outstanding basic, translational and clinical research and training, integrated with many of the programs and core services of the CCTSI. The **CU College of Nursing (CON)** is the premier nursing school in the Rocky Mountain West and is best known as the birthplace of the nurse practitioner, and for research in community outcomes, informatics, and human caring. CON trainees and faculty will have major involvement in the Clinical Science PhD graduate program, informatics and the Community Engagement and Research activities of the CCTSI. The **CU Skaggs School of Pharmacy and Pharmaceutical Sciences (SOP)** is consistently ranked among the top pharmacy graduate programs and ranked 5th in NIH funding in 2016. The school has developed

a cutting-edge Medicinal and Translational Pharmacology Program, including a molecular modeling facility with computerized macromolecular structure analysis and drug design, high throughput and high content compound screening and medicinal chemistry cores, all of which are supported within the T1 CTR Resources and Services Program of the CCTSI. The **CU School of Dentistry (SOD)** is the preeminent dental school within the Rocky Mountain West Region. The School pioneers research in oral cancer, Native American oral health, salivary gland disease, neurobiology, pain control and tissue engineering. The **Colorado School of Public Health (CSPH)** was created in August 2007 as a partnership between CU-D, CSU and University of Northern Colorado. The CSPH plays a major role in the training programs and T3 and T4 translational research programs within the CCTSI, and houses the CCTSI Biostatistics (BERD) Program. **CU-D Graduate School** offers 21 PhD graduate programs and five Masters programs. PhD degrees may be obtained in multiple basic and clinical science fields (including the Clinical Science PhD program). Within this program is a long-standing highly successful Medical Scientist Training Program (MSTP). The CCTSI pre-doctoral TL1 program has funded 8 PhD students each year and encourages the application of basic techniques to study human health and disease processes through novel coursework and interdisciplinary interactions. The **CU-D, Downtown Denver Campus** is a comprehensive urban university which offers bachelor to doctoral degrees in the full spectrum of liberal arts and professional fields. The School of Education and Human Development houses our Tracking & Evaluation Core and faculty from the School of Engineering and Applied Sciences, and the College of Liberal Arts and Sciences have joined as CCTSI Members.

- **UNIVERSITY OF COLORADO AT BOULDER (CU-B)** is a premier academic and research University, including 8 schools and colleges and 44 doctoral degree programs. With 5 Nobel Laureates on the faculty, there is a rich history of innovative discovery leading to human applications in fields of biotechnology, medical research, biochemistry, biology, and engineering. Interdisciplinary collaboration between CU-B and CU-D investigators has led to major discoveries in bioengineering, tissue engineering, congestive heart failure, congenital heart disease, the microbiome, pharmaceutical biotechnology, and molecular biology. The new BioFrontiers Institute, directed by Nobel Laureate Thomas Cech, employs a unique interdisciplinary team of scientists with laboratory adjacencies and cutting edge biotechnology. A CCTSI CTRC is located at CU-B. One of the major CCTSI goals will be to expand collaborative interdisciplinary research and training programs between CU-B and CU-D. *The VC of Research has provided a letter of support.*

- **COLORADO STATE UNIVERSITY (CSU)** is the **newest official partner university** in the CCTSI, joining he CCTSI in 2013. CSU is a public land grant institution founded in 1870 located in Fort Collins, a midsize city one hour north of Denver. CSU includes 8 colleges, including the renowned College of Veterinary Medicine and Biomedical Sciences. CSU is considered one of the leading research universities in fields such as animal sciences, atmospheric science, infectious diseases, clean energy technologies, and environmental science. Collaborative research and education programs have taken place for decades between CSU faculty and CU-D and CU-B faculty. CSU is a partner in the CU Comprehensive Cancer Center (NCI), the Nutrition and Obesity Research Center (NIDDK), and the CSPH, with major CU-D research collaborations in infectious disease, exercise physiology, HIV/AIDS research, community engagement and research. CSU partnership in the CCTSI will expand the use of natural animal models of human diseases in translational research projects, bridging across CCTSI

institutions. *The Vice President of Research has provided a letter of support*.

HOSPITAL AND HEALTH CARE ORGANIZATION PARTNERS

NOTE: All researchers at the following hospitals have faculty appointments at CU-D.

University of Colorado Hospital (UCH), located on the AMC, is a private, not-for-profit hospital for adults and is one of the primary teaching hospitals for CU-D. UCH is consistently ranked among the top hospitals in the country by *US News and World Report* and the University Health System Consortium. The new facilities include a 673 bed hospital, the Anschutz Outpatient Pavilion (550,000 outpatient visits annually), and the Anschutz Cancer Center. UCH is dedicated to research and quality improvement in clinical care. CCTSI CTRCs are located at UCH. Will Cook, UCH President, commits his full support to the CCTSI and CTRCs (*see letter of support*).

University of Colorado Health System (UC Health). Created in 2011, this *newest and largest health system* in Colorado combines UCH with 5 other hospitals in the front range of Colorado and southern Wyoming, totaling >1,800 hospital beds and 1.5 million outpatient visits. Unprecedented opportunities for expanding clinical trials, personalized medicine and community-based research will unfold over coming years as a single electronic medical record (Epic) is being installed in all of the hospitals. The CCTSI will play a major role in developing and integrating clinical research infrastructure, data sharing and training across UCHealth.

Children's Hospital Colorado (CHCO), one of the preeminent academic pediatric healthcare institutions in the nation, is a private, not-for-profit independent hospital with a strong affiliation with CU-D. CHCO, consistently ranked in the top 10 Children's Hospitals by *US News and World Report*, relocated to its new 1.4 million ft^2 facility at AMC in 2007, putting it in close proximity for the first time to the health science schools, UCH, and the CU-D training and research facilities. With hospital expansion, total inpatient beds now exceed 440, with 15,000 inpatient admissions and over 500,00 outpatient visits per year. CHCO is home to most of the child health research performed at CU-AMC, in large part because of a 55-year history of a separate pediatric GCRC and CTRC at CHCO. The CHCO CTRC has received substantial support including over 22,000 ft^2 of rent-free space at CHCO. The CHCO Research Institute works closely with the CCTSI. Jena Hausmann, President and CEO of CHCO, has pledged his support to the CCTSI (see *letter of support*).

National Jewish Health (NJH) is known world-wide for ground-breaking basic and translational research and treatment of respiratory, immune, and allergic disorders. NJH is a non- sectarian, not-for-profit academic hospital which has been ranked #1 in respiratory diseases for 15 consecutive years by *US News and World Report*. NJH is primarily an outpatient facility. NJH and CU-D collaborate extensively on training and research, with shared fellowships, co-investigators on grant applications, and shared core facilities. NJH faculty receive *over $46 million in annual research funding ($33 million from NIH) in 2016*. A CCTSI CTRC unit and Core Lab facilities have been housed at NJH for the past 18 years. Building on these, NJH has launched three personalized medicine centers that are integrated with the CCTSI: an Integrated Bioinformation and Specimen Center, an Integrated Center for Genes, Environment and Health, and a Center for Advanced Diagnostics. Michael Salem, MD, President and CEO of NJH, has pledged his ongoing support to the CCTSI (*see letter of support*).

Denver Health (DH), a premier safety net hospital, provides healthcare for over 25% of all residents in the City of Denver. DH is a comprehensive, integrated health care organization, including a 477 bed hospital, the Denver Public Health Department, an 11-site network of school-based health centers in the Denver Public Schools, correctional care, and a 9-clinic network of family health centers throughout the city of Denver. DH admits over 25,000 patients per year, and administers over 450,000 outpatient visits. DH faculty of the SOM have been international leaders in trauma and surgical research, health outcomes research, community translational research and informatics technology, and HIV prevention and treatment. Robin WIttenstein,, the President and CEO of DH, has committed partnership and support for the CCTSI (*see letter of support*).

Denver Veteran's Affairs Medical Center (DVAMC) is a training site for CU-D residents in all adult specialties. The DVAMC will relocate in 2018 to a new 182 bed 1.1 million ft^2 facility on the AMC

(**Figure**), bringing the three major CU-D teaching hospitals to the same campus for the first time. Supported by *over $58 million of grant funding*, DVAMC conducts major clinical and translational research in cardiovascular epidemiology, gastrointestinal cancer, chronic hepatitis, mental health, neurodegenerative diseases, diabetes, substance abuse and geriatrics. DVAMC faculty hold leadership positions within the CCTSI. Sallie Houser-Hanfelder, Director of DVAMC, has pledged her support and continued CCTSI partnership (*see letter of support*).

Kaiser Permanente of Colorado, Institute for Health Research, (KP), directed by John Steiner, MD, Professor of Medicine, is the research arm of KP in Colorado, and employs over 120 investigators and staff receiving *over $20 million of extramural funding* for active projects that focus on advancing preventive health care and personalized lifestyle changes to improve population health, community-based clinical trials, and improving process and health care delivery. KP investigators will play major roles in the community engagement and research, translational informatics, study design and biostatistics, and research training, functions of the CCTSI. Roland Lyon,, President of Kaiser Foundation Health Plan of Colorado, has committed support to the CCTSI (*See letter of support*).

COMMUNITY ORGANIZATIONS AND PARTNERSHIPS..

Through the CCTSI Community Engagement & Research (CE&R) program, sustained relationships with over 30 community organizations have been established. The Partnership of Academicians & Communities for Translation (PACT) is the governing body of the CE&R program and is a statewide collaborative of academic researchers, community-based organizations, PBRNs and healthcare provider networks working together to provide a platform for innovation in CE&R. The PACT is governed by an 18 member Council, meeting quarterly, with equal representation from communities and from the academic institutions. Among the PACT members is the Shared Network of Colorado Ambulatory Practices & Partners (SNOCAP), which includes 7 large PBRNs which cover the state of Colorado and have performed over 80 research studies. PACT organizations cover nearly 300 physician practices, 30 hospitals and one million individuals, representing rural, underserved and minority populations.

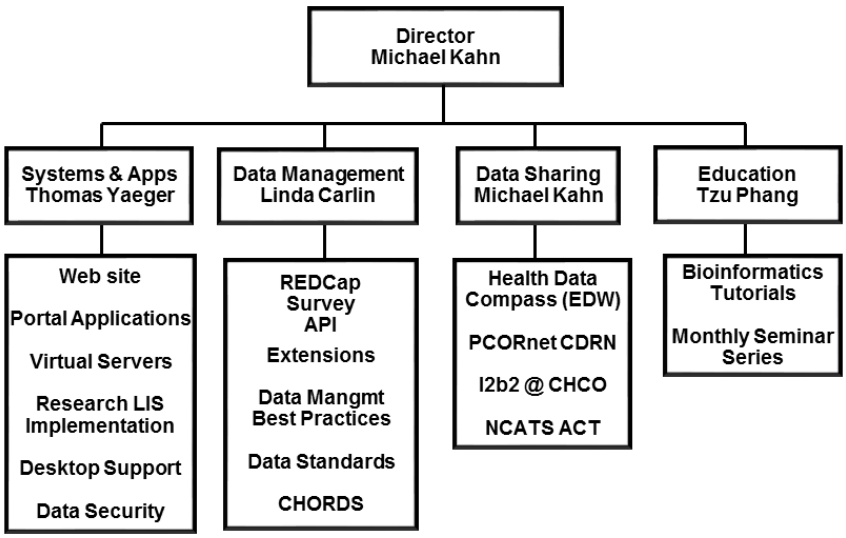
2. UNIQUE INSTITUTIONAL ASSETS

The CCTSI will achieve our 5 Strategic Goals by capitalizing on a set of unique attributes that differentiate the CCTSI program. These attributes include:

1. An extensive **Translational Workforce Development and Education program** spanning from high school students through senior faculty. TWD's 11 educational programs include the well-established (in 1999) successful **Clinical Science PhD and Masters Programs**, one of the first such programs in the nation.
2. One of the first **Centralized IRB models in the nation** (Colorado Multiple Institution Review Board; COMIRB), now being the sole IRB of record for five of our partner institutions with established agreements with 160 entities, and has participated in ceding to other central IRBs numerous times. CU-D has signed onto the SMART IRB from NCATS and will participate in singe/central IRB-supported studies as required. COMIRB has also ensured a high level of data security by mandating the use of REDCap or similar databases for data storage in all clinical research protocols.
3. A strong tradition of high impact clinical research supported by a robust **network of 5 Clinical Translational Research Centers (CTRCs, our clinical research units)** continuously funded for >55 years (first as GCRCs and now as CTRCs), among the busiest among current CTSA Hubs. The CTRCs will be the sites for many of the Trial Innovation Network supported multi-site NIH trials in the future.
4. Robust **Academic-Community partnerships** and **Practiced-Based Research Networks** throughout the state of Colorado in our **Partnership of Academicians and Communities for Translation (PACT)**.
5. An expanding **Biomedical Informatics Infrastructure,** the direct result of CCTSI initiatives, including a new academic Division and the Center for Personalized Medicine at CU-D, and a multi-instituional Research Data Warehouse (Health Data Compass).

6. A unique **Naturally Occurring Animal Model Core** based at the CSU College of Veterinary Medicine, in which naturally occurring animal models of human disease, sharing similar biology, are utilized to test new diagnostics, imaging technologies and clinical trials of therapeutics before initiating human studies, thus reducing risk for human subjects in early phase development. We have labeled this pre-clinical translational research as phase *T0.5*. This Core will provide a rich environment for interdisciplinary team science.
7. Longstanding **Child and Maternal Health Research Programs** nationally recognized for innovation in therapeutics development and prevention of key disorders of childhood.
8. A mature affiliated network **of six academic hospitals and health care organizations** which have worked collaboratively for decades to establish outstanding health professional training and research programs that bridge across diverse populations. In addition, the recently established and growing UC Health system, a network of 6 hospitals in Colorado and Southern Wyoming (including University of Colorado Hospital at the AMC) which share a single electronic medical record (Epic), creates new opportunities for data sharing, expansion of clinical trials, personalized medicine and outcomes research.
9. The **Medicinal Chemistry and Translational Pharmacology program** within the CU School of Pharmacy, which opened in 2010, with high throughput/content screening, computer modeling and therapeutics optimization and synthesis capabilities.

TRANSLATIONAL INFORMATICS: FACILITIES AND OTHER RESOURCES



The Translational Informatics function of the CCTSI develops research informatics tools and provides training and support for research informatics needs. The Data Management team has implemented and oversees REDCap, a web-based, HIPAA-compliant study data management solution that is straightforward and robust and being adopted widely by members of the national CTSA consortium. Through SeDLAC (Secondary Database Library and Analysis Center), CCTSI members have access to large national population-based datasets from NCVS and AHRQ. The System Services team maintains approximately 20 servers running several applications, at the department and enterprise level, for data management needs across the CCTSI. In addition, System Services manages backups, security, networking, access controls, desktop support for the CCTSI administration core and CTRCs, and CCTSI website development.

CCTSI website

The CCTSI website (http://cctsi.ucdenver.edu) acts as the portal of entry for faculty, trainees, research associates, other university personnel, the public and the private sector to gain access to services and resources, applications, RFAs, training opportunities, success stories, and announcements about our programs. The website receives over 4,200 visits per month accessing over 14,000 page views. CCTSI membership is required to utilize services and training programs, with membership exceeding 4,350 as of May, 2017. Membership is available to faculty, trainees, research associates, community members and the private and public sectors and is obtained through an online registration form. COLORADO Profiles, a web-based searchable faculty biomedical research database for the entire University of Colorado system (http://profiles.ucdenver.edu) managed by the Informatics Core of the CCTSI, receives over 10,000 visits per month for over 40,000 page views.

Health Data Compass

Health Data Compass (Compass) is a multi-institutional data warehouse funded by the University of Colorado Health System, Children's Hospital Colorado, CU Medicine (formerly UPI), and the University of Colorado School of Medicine. Unlike existing data resources in these institutions, Compass is specifically designed to support data discovery and data sciences methodologies that integrate, harmonize, and link large-scale biological, clinical, administrative, regional, state and national data sets, such as environmental exposures and CDC national data sets (Figure 1). Compass currently contains inpatient and outpatient data including patient, encounter, diagnosis, procedures, medications and laboratory results (see http://healthdatacompass.org → Available Data). New initiatives include text extraction from structured reports and natural language processing (NLP) techniques for concept extraction from unstructured data. Using both traditional relational database technologies and novel cloud-based non-relational database architectures, Compass is specifically focused on developing efficient data acquisition, processing and linkage methods to create unique data sets organized for data analytics and visualizations. For example, we have developed new record linkage methods that have superior performance over existing methods when linkage variables are

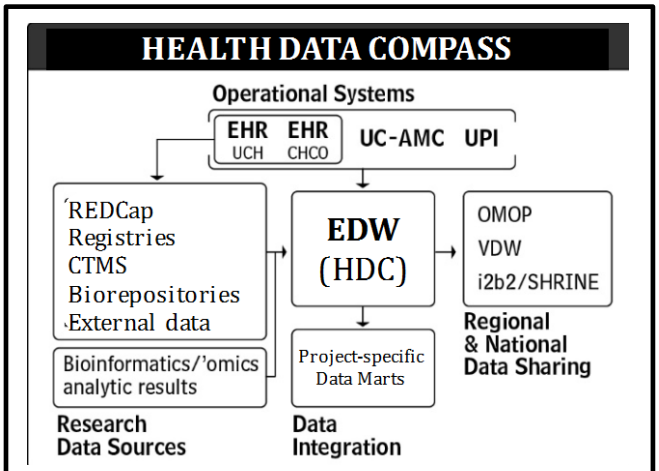


Figure 4: Data sources, integration and sharing capabilities of Health Data Compass.

missing or corrupted[115]. Many of the core large-scale skills and technologies used in the development of national data sharing networks previously described are being reused and expanded by Compass. By design, Compass has been architected to accept data from disparate data sources and has established a processing pipeline to incorporate these new data sources into the Compass warehouse. We will leverage this mature set of processes to incorporate data from the highly dispersed and heterogeneous data sources across the RMPMI cohort.

Patient data is integrated into the Compass enterprise data warehouse through processes developed by specialized engineers to extract data from various source systems, transform that data into a common schema, and load the data into the data warehouse. The source data systems include clinical operational systems like EHRs, research databases, biorepositories, and processed *omics data (VCF files). The integration of these disparate data is linked to create a longitudinal patient record. Relevant clinical and *omics data is then extracted into data marts that allow for easy queries to be made for the relevant research projects. The Compass enterprise data warehouse utilizes a variety of technologies to link phenotypic and molecular data, allowing end-users to execute queries that combine clinical and *omics attributes.

Compass is housed on the Anschutz Medical Campus of the University of Colorado Denver in Aurora, Colorado. The Compass office provides 1800 sq. ft. of private office and conference room space for personnel. The Compass data warehouse consists of a variety of on-premises and cloud-based computing resources that will be allocated in support of this project depending on the specific technical demands of the project and the participating clinical sites. These resources include a 24-core Oracle Exadata database server with 512GB RAM and over 70TB storage; a stack of 12-core, 256GB Sun servers for middleware and web applications. Compass resources are hosted within the University of Colorado's Office of Information Technology data center, a 2000 sq. ft. secure environment constructed specifically to support mission critical servers and equipment. Physical access to this server is badge-controlled and tightly defined to a list of critical personnel (2-3 people) to ensure tight security. PHI data stored on this server is not accessible to any end-user until it has been fully integrated from the source systems, transformed into the proper data model, and then subsetted into data marts which are then made available to for end-users to query. The Compass informatics environment is hosted and operates as a HIPAA-compliant solution for storing and accessing sensitive PHI data. In addition, Health Data Compass has legal and regulatory agreements in place with Google for use of their massively scalable Google Cloud Platform, including next-generation data integration and analysis platforms like Google BigQuery and Google Genomics.

AMC Computational Resources

Anschutz High Performance Computing Exchange (AHPCE)

The Translational Informatics and Computational Resource (TICR) is an integral component of the Colorado Center for Personalized Medicine (CCPM). This in-house, comprehensive, stand-alone biocomputing unit supports a multidisciplinary, robust computing resource to foster omics-based research using high-dimensionality data (*e.g.*, genomics, transcriptomics, microbiomics, proteomics, metabolomics) and development and implementation of computational methods and tools for sequence analysis and systems biology approaches.

Computer Cluster

The Translational Informatics and Computational Resource (TICR) computer cluster is designed with a minimum of 768 cores (Xeon E5-2680 v3 at 2.5Ghz), 4TB of RAM and 3.7 PB of useable storage. This cluster includes all necessary HPC components, including but not limited to a scheduler (SLURM), manager nodes, master nodes, login nodes, compute nodes, storage and cluster management software. The storage array is designed to provide a minimum of 3.7 PB of useable data storage for both home directories and scratch, using IBM General Parallel File System (GPFS). The processing network for the compute cluster consists of Infiniband switches, providing a low latency and high bandwidth interconnect for parallel computations and storage access. The compute cluster has redundant 10 gigabit Ethernet connectivity to OIT's current network core and management switches, and can easily expand both in terms of network, compute and storage capacity based on need.

Application Cluster

The HPC environment also includes an application cluster, which consists of six physical servers running VMware vSphere virtualization, plus a dedicated fibre channel SAN. The application cluster is designed for redundancy and high availability. Each server has a minimum of 36 Xeon v3 cores at 2.3Ghz and 256GB of

RAM. The fiber channel SAN is dedicated to the application cluster and includes 30TB of solid state disk. This array is able to be easily expanded to support future storage growth. The application cluster has redundant 10 gigabit Ethernet connectivity to OIT's current network core and management switches, and can be easily expanded in terms of computation resources and storage.

High Memory Nodes

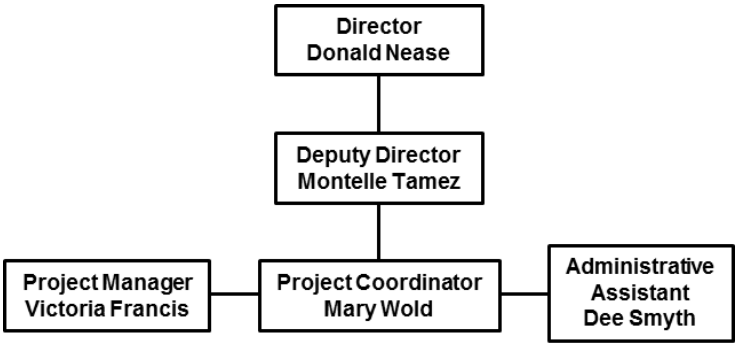
The TICR compute cluster currently includes one additional high memory compute node with 36 Xeon v4 cores and 1.5 TB RAM, to support high memory workloads such as experimental sequence alignment techniques.

Back-Up Solution

A file-level end-to-end back-up solution will be implemented with initial back-up requirements of 500 TB of protected data, with a design optimized for long term retention.

COMMUNITY AND COLLABORATION: FACILITIES AND OTHER RESOURCES

Community Engagement and Research Program (CE&R)



The CCTSI has integrated community-based participatory research (CBPR) into programs that engage the wider community with research into the causes and remedies of health problems and disparities in underserved populations in Colorado and the nation. It has built on a rich history of practice-based and community-based research in the state, which now includes 18 established community-academic partnerships. These partner communities include rural and urban populations, American Indian and Alaska Native, Hispanic and African American groups, providing a unique opportunity for culturally proficient research emphasizing health disparities. The innovative Partnership of Academicians and Communities for Translation (PACT) brings academic/community partnerships into a sustainable and collaborative balanced (equal numbers of community members and academicians) governance group for bidirectional exchange, and fostering public trust in the research enterprise. PACT oversees a variety of activities, including 8 Community Research Liaisons, the Community Immersion Program, Bootcamp Translation program, CE Pilot Grants, community forums and other activities described more fully in the Community and Collaboration section of the grant application.

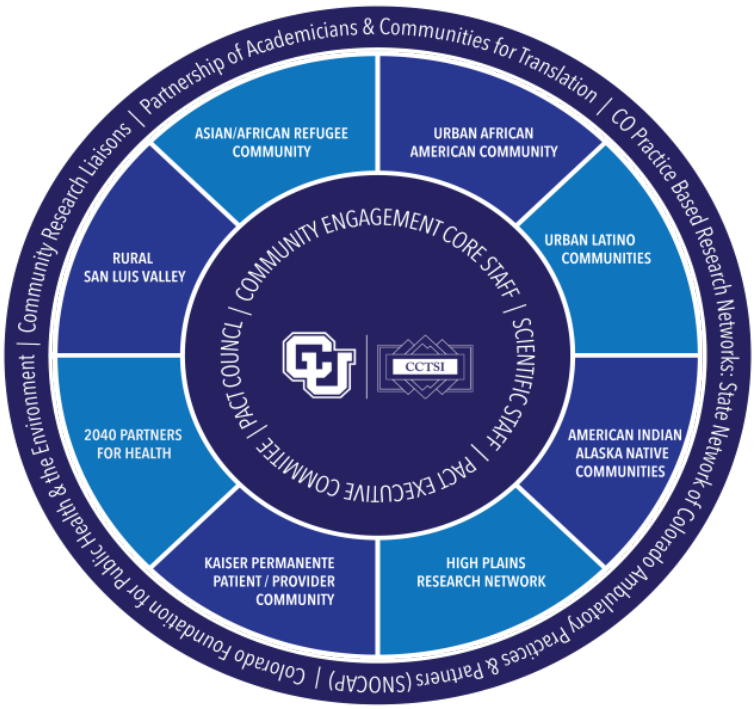
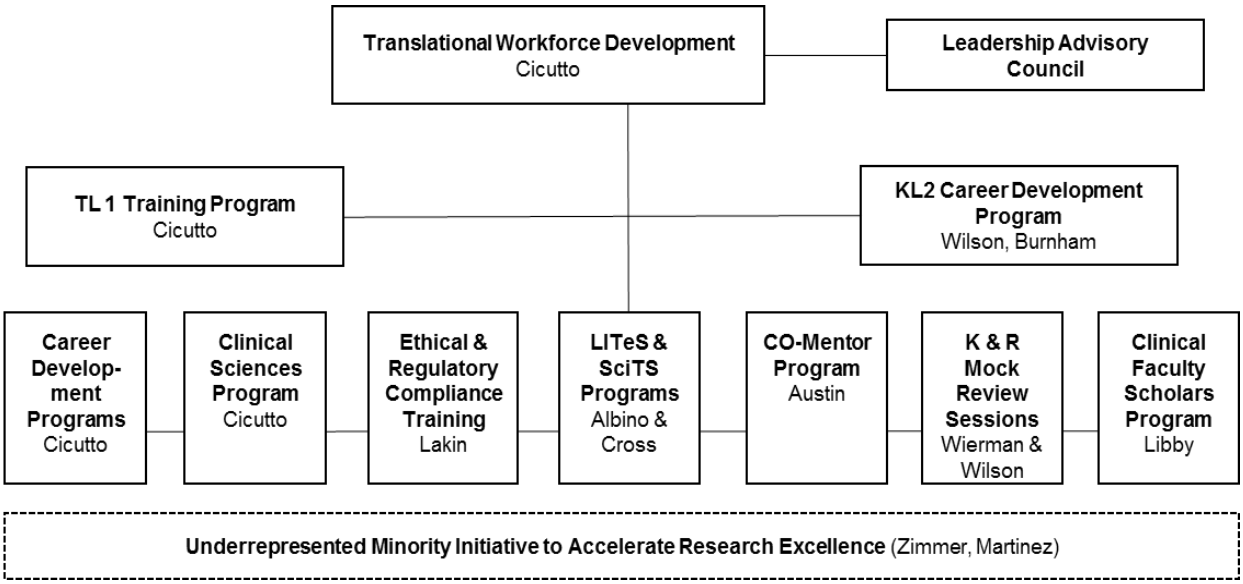


Figure 2. CE&R PACT Council Partners and Structure.

TRANSLATIONAL WORKFORCE DEVELOPMENT (TWD): FACILITIES AND OTHER RESOURCES



The TWD program provides clinical-translational scientists and trainees with knowledge, training, and career skills. TWD offerings span critical periods, from the beginning of research training at the pre-doctoral level through senior faculty. The aim of the TWD is to create a robust local workforce and a national leadership pool for clinical-translational research who are interdisciplinary, innovative, and highly motivated and successful. TWD leverages and integrates educational programs at CU-D and its partners, to provide skills training in strategic areas. Programs are intended to promote innovation and team collaboration, leading to research with broad implications for public health. A cadre of faculty, educators, and administrative staff are dedicated to providing programs of the highest quality. The TWD provides a broad menu of training and career development opportunities.

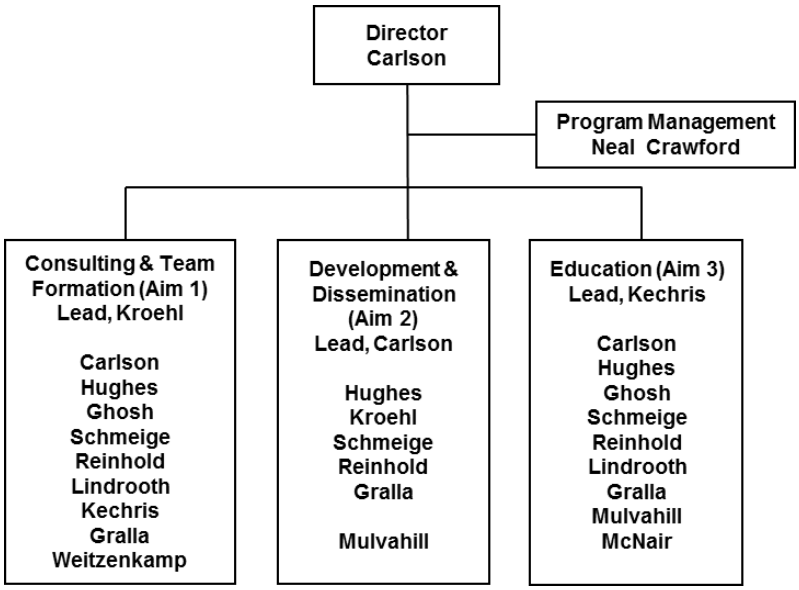
Programs

- TL1 Training program. This program provides integration between current training in molecular, cellular, and/or behavioral science, and whole body physiology and disease processes with clinical experience. Candidates are actively co-mentored by faculty with basic science and clinical research experience. This program currently has enrolled 8 PhD students each year but will be expanded and enhanced under the new award and will enroll up to 15 pre- and post-doctoral trainees per year with an emphasis on underrepresented minorities, and now to include students from Colorado State University.
- KL2 Mentored Career Development (Research Scholar) program. This program provides up to 3 years of funding for clinical translational research, education and mentored career development to train awardees in the optimal conduct of translational research with the ultimate goal of obtaining individual peer reviewed grant funding. This program supports 5 junior faculty at any one time.
- Clinical Sciences Graduate Program (CLSC). One of the first Clinical Sciences Graduate Programs in the country, this program awards MSCS and PhD degrees in 3 distinct specialty tracks: Clinical Investigation, Health Services Research, and Health Information Technology. This program enrolls 110-115 students at any given time and aims to train nationally competitive clinician/clinical translational scientists by providing a formal and structured educational and mentoring program. Graduates are trained to conduct rigorous and relevant patient-based research within stringent ethical and regulatory guidelines, and translate the evidence for community application. In addition, more than 200 other non-degree students attend CSLC classes each year.
- Clinical Faculty Scholars Program for developing junior faculty research independence. This program enrolls 4-5 learners per year and aims to help emerging investigators obtain a career development award (K08, K23 or foundation equivalent), or a first independent, extramural project award (R21, R01 or equivalent) through guided project development, educational seminars, grant writing classes, and mentorship. Each Faculty Scholar develops an individual career development plan and receives regular individual mentorship from four experienced senior researchers. This program acts as a pipelineof promising individuals into the KL2 program.

- Leadership in Team Science (LITeS) program is a yearlong program for mid-level and senior faculty to enhance leadership skills, foster team science by creating a network of colleagues who serve as resources for one another, expand opportunities for cross-disciplinary collaboration, and ensure that clinical and translational scientists have the skills for effective team leadership. To date, LITeS has trained over 200 participants including deans, associate deans, department chairs, vice-chairs, and section heads, as well as senior leadership from hospitals, major research centers, and training programs. This program competitively enrolls 20-30 participants per year to work on solutions to high-level issues chosen by UCD leadership.
- Mock study section and grant review programs. These programs utilize mock study section pre-review of grants prior to formal submission. Participants of this program receive insight into the grant review process and help to improve the science and format of their applications thereby increasing their chances for success.
- Colorado Mentoring Training (CO-Mentor) training is a six day program which utilizes evidence-based strategies to teach mentor/mentee pairs the skills they need to get the most out of their mentoring relationships and develop the mentoring potential of their mentees.
- Clinical Research Education Program: Curriculum to improve regulatory knowledge and compliance and GCP and RCR application. Provides required regulatory courses (GCP,RCR, human subject protection including informed consent) for all people involved in CTR Variety of training forums: seminars, courses, individual consults, online modules. Over 700 attendees annually.

RESEARCH METHODS: FACILITIES AND OTHER RESOURCES

Biostatistics, Epidemiology, and Research Design (BERD) Core



The BERD Core allows CCTSI members to collaborate and consult with biostatisticians who can assist with study design, grant writing and planning of biostatistical analysis. The actual analysis of data is not funded by CTSA grant funds, but rather from funding of individual research grants and studies. The one exception is for Junior investigators without substantial grant support, who can apply for CCTSI *Microgrants* that can offset some of the costs of the statistical analysis. BERD provides innovative training programs in biostatistics for non-statisticians. As part of the Colorado School of Public Health (CSPH), whose core mission is to promote the physical, mental, social and environmental health of people and communities in the Rocky Mountain Region and globally, BERD leverages and integrates CSPH and CCTSI resources.

Computer

The CSPH at the University of Colorado Denver is equipped with over 160 computers and work stations. CSPH faculty have computers and laser printers for their use. University computing facilities provide access to e-mail, Internet, and bibliographic databases. Information technology specialists are available on a fee-for-service basis through the CU Denver Workstation Support Center. The institution has also invested in a high performance computer network, Rosalind. This is available on a fee-per core hour used. Rosalind is composed of 768 cores, 4 TB of RAM (128 GB RAM per node), 3.7 PB of usable storage and a high memory node with 1.5 TB of RAM. This in-house, comprehensive, stand-alone biocomputing unit supports a multidisciplinary, robust computing resource to foster omics-based research using high-dimensionality data (e.g. genomics, transcriptomics, microbiomics, proteomics, metabolomics) and development and implementation of computational methods and tools for sequence analysis and systems biology approaches.. To conduct rigorous and reproducible analyses, the Colorado Biostatistics Consortium and Department of Biostatistics and Informatics of the CSPH will conduct statistical analyses for larger projects.

Office

BERD space is primarily located within the CSPH in Buildings 500 and 406 on the Anschutz Medial Campus. Building 500 comprises 25,410 square feet of state-of-the-art office space with Building 406 providing more than 30 additional offices. The school provides basic furniture, fax machines, copiers, and non-research related office supplies. In addition, the CSPH facility provides meeting and conference rooms, with video conferencing capabilities, that can be scheduled for project use as needed. The Colorado Biostatistics Consortium and the BERD (which shares office space with the Colorado Biostatistics Consortium) have individual offices in Building 406 for 10 of the faculty members. Building 500 provides an individual office for 5 of the other faculty members in their respective Departments. The project managers in the BERD are housed in Building 406 adjacent to the Director (Dr. Nichole Carlson).

Scientific Environment

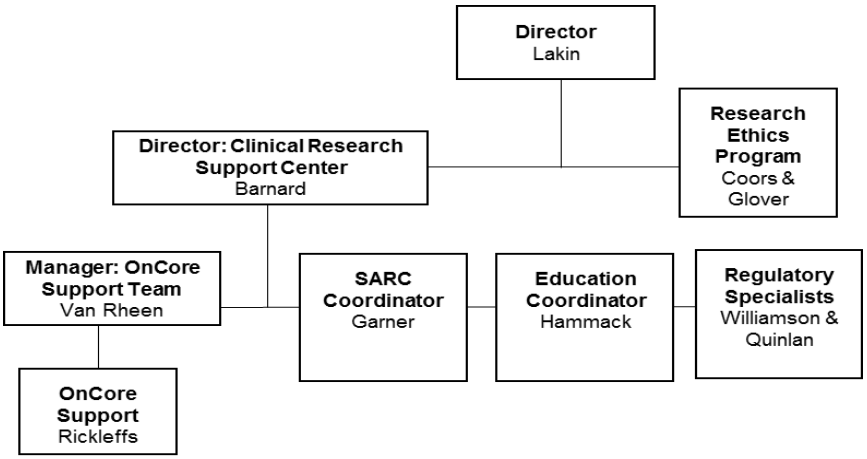
In July 1, 2008, the newly established CSPH was the first and only school of public health in the Rocky Mountain Region, attracting top tier faculty and students from across the county, and providing a vital contribution toward ensuring our region's health and well-being. Collaboratively formed by the University of Colorado Denver, Colorado State University and the University of Northern Colorado, CSPH provides training, innovative research and community service to actively address public health issues, including

chronic disease, access to health care, environmental threats, emerging infectious disease, and costly injuries.

Colorado Biostatistics Consortium (CBC)

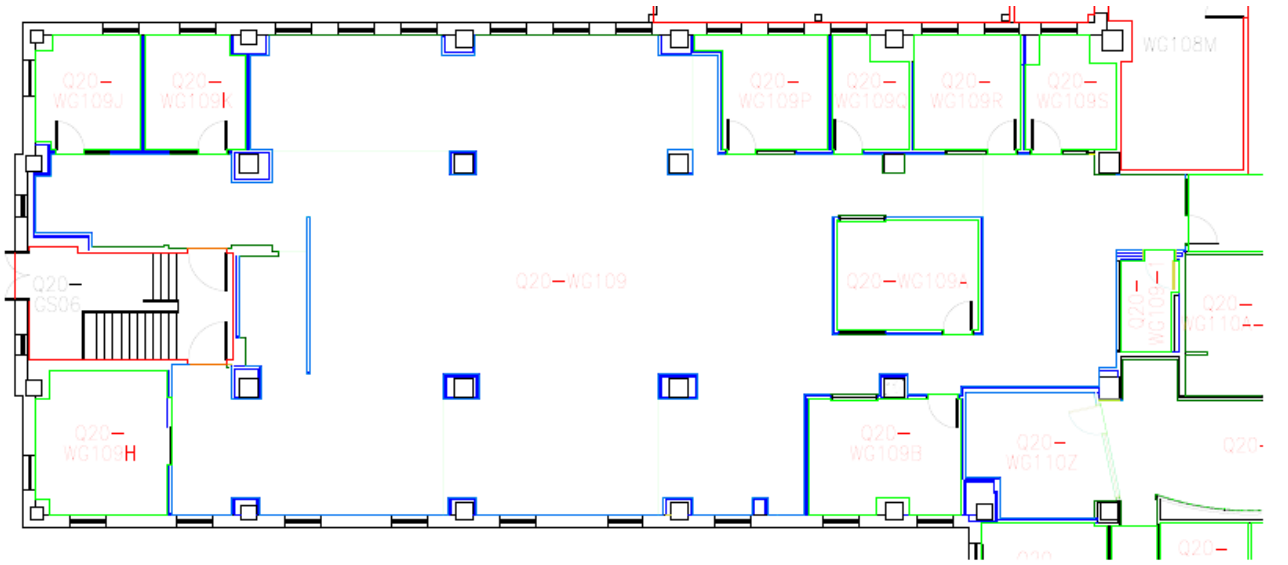
The CBC is a campus wide resource for establishing and supporting collaborative and consulting relationships with clinical and health researchers, primarily at the Anschutz Medical Campus. The CBC resides in the Department of Biostatistics and Informatics of the CSPH and has 10 PhD faculty, three MS faculty, and several graduate student research assistants. All have academic appointments in the Department of Biostatistics and Informatics and a subset of the faculty and MS participate in the BERD. The range of expertise is substantial and varied. Some areas include: Bayesian modeling, clinical trials, causal inference, spatial modeling, SEM and mediation analyses, microbiome, and 'omics (RNAseq, methylation, proteomics, metabolomics among others).

Research Methods:
Regulatory Knowledge and Support Core (RKS)



RKS helps CCTSI members navigate through regulatory requirements and provides training and consultation in the responsible conduct of research. The RKS and CRAO share 5,000 sq ft of office, conference room, and collaboration space on the ground floor of Building 500 at the Anschutz Medical Campus. This consists of 3 conference rooms, 27 cubicles, 4 offices, a storage room, a communal lunchroom, and collaborative spaces including open, communal printer/ copier and seating areas. This "google-style" space houses RKS staff as well as staff from UCD contracting, CCTSI Scientific and review Committee (SARC) and research education, the Trial Innovation network (TIN), CU Innovations, OnCore team members, and UCH billing. This novel arrangement, housing parties within a functional cross-institutional team space rather than in space assigned by each staff member's employer spread over campus, facilitates collaboration and direct access to the knowledge and expertise necessary to assimilate information quickly, brainstorm and resolve problems in real time, and provide solutions, workflows, and training opportunities that are consistent across AMC. In addition, RKS space is the same building as many entities essential for the safe and efficient conduct of translational research such as COMIRB, other regulatory office, and the Dean's Office, which provides further team building and collaboration opportunities.

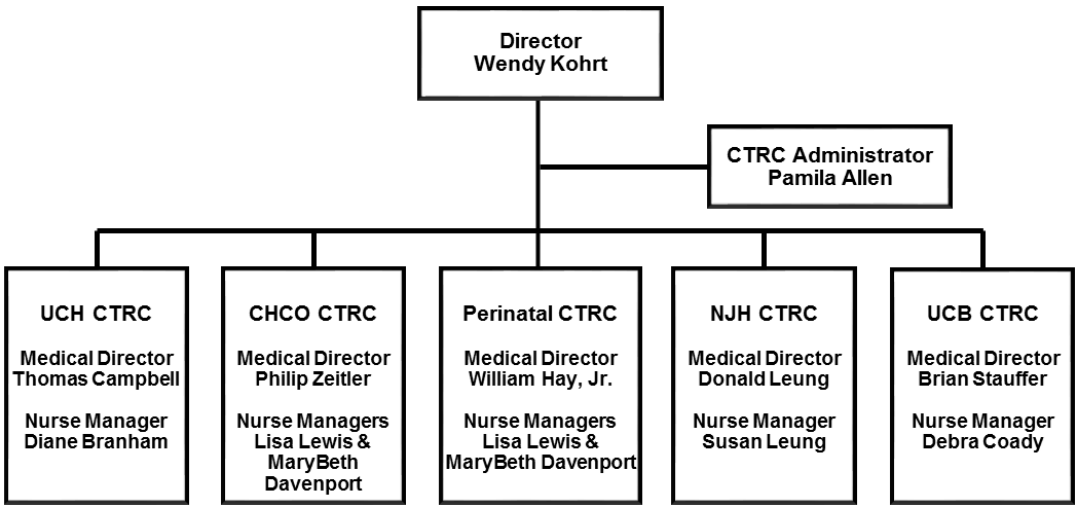
Figure 3. RKS space with dedicated areas for interaction and collaboration.



FACILITIES AND OTHER RESOURCES

HUB RESEARCH CAPACITY: PARTICIPANT AND CLINICAL INTERACTIONS

Clinical Translational Research Centers (CTRCs)



Our network of 5 Clinical Translational Research Centers (CTRCs; our clinical research units) provides inpatient and outpatient research facilities. The CTRCs have their original foundation in the enormously effective Adult and Pediatric GCRC facilities, which were continuously NIH-funded for 46 and 45 years, respectively, before the NIH transitioned the GCRC grant program to its CTSA initiative. The CTRCs have been transformed since this transition and now provide resources for all phases of clinical trial development and conduct, critical care (adult and pediatric), and expanded multidisciplinary coordinated clinical research support. CTRC facilities are provided at University of Colorado Anschutz Medical Campus (UCH and CHCO), University of Colorado Boulder, National Jewish Health, and a mobile perinatal unit at several hospitals. Available CTRC resources include dedicated inpatient and outpatient research space and equipment, expert research nursing, Core laboratories, and nutrition services. An additional mobile Perinatal CTRC operates at UCH, CHCO and Denver Health to facilitate research in pregnant women and newborns. All CTRC services are available to investigators on a fee-for-service basis, since 2015.

Anschutz Medical Campus (AMC)
University of Colorado Hospital (UCH) CTRC
Facility

The UCH CTRC provides the space, staff, and equipment necessary to conduct a broad range of specialized research procedures in primarily adults, including measurement of insulin sensitivity (insulin and glucose clamps, OGTT, IVGTT), body composition measurements, medication administration and infusions, bronchoscopies, fat and muscle biopsies, VO_2max and graded exercise tests, echocardiography for vascular and cardiac studies, sleep studies (acute and chronic) with polysomnography, measurement of total energy expenditure and rates of macronutrient utilization, conduct of short- and long-term exercise and dietary intervention studies, and specimen collection and processing. All procedures are supervised by highly-qualified and experienced personnel. All staff receive HIPAA and Good Clinical Practice training. Nurses are Basic Life Support (BLS), Advanced Cardiac Life Support (ACLS), and ONS (Chemotherapy) certified. Health technicians are BLS certified.

The UCH CTRC has 7,226 sq ft of inpatient space located on the 12th floor of UCH at the Anschutz Medical Campus, has seven beds in five rooms, and a wet lab for sample processing. Additional unique resources include an inpatient whole room calorimeter for the measurement of 24-hour energy expenditure and substrate oxidation, and a sleep laboratory with adjacent monitoring space for polysomnography. Experienced research nursing and health technician support is available.

The UCH outpatient CTRC consists of 6,000 sq ft of space, which houses an outpatient research clinic. Facilities in the clinic include an infusion room (5 chairs), phlebotomy room (5 stations), exercise testing room (3 stations), muscle function room (isokinetic dynamometer), body composition room (DXA, pQCT), secure medication storage room (approved for FDA controlled substances, including Schedule 1), sample

processing room, negative pressure room, 2 interview rooms, 2 large procedure rooms with beds, 4 small procedure rooms with beds (including one for RMR and one for echosonography), and 8 exam rooms with exam tables. There is a charting/work area with 5 computer work stations that can be used by research team members. An adjacent 3,200 sq ft state-of-the-art research exercise training facility is available for exercise intervention research. The CTRC also includes a Bionutrition core, special metabolic kitchen, and a core laboratory. The CTRC clinical outpatient facility is generally open weekdays 7am – 6pm. During these hours, experienced physician assistant, research nursing, health technician, laboratory, and nutrition support is available. Outpatient visits that occur outside of regular opening hours can sometimes be accommodated by inpatient CTRC nursing staff.

The UCH CTRC has 11.4 FTE of research nurses, 1.5 FTE of health technician support, a 1.0 FTE sonographer (shared between UCH and CHCO CTRCs), a 1.0 FTE physician assistant, 0.3 FTE DXA technician, 4.4 FTE of nutrition and metabolic kitchen staff, and 3.6 FTE of core laboratory staff support. These research professionals have extensive experience in conducting and documenting research for a diverse patient population from 12 to 90 years of age, both healthy and with a range of diseases such as diabetes, obesity, cardiovascular disease, renal disease, COPD, HIV and AIDS, chronic viral hepatitis, various forms of cancer, alcoholism, etc.

Children's Hospital Colorado (CHCO) CTRC

Facility

The CHCO CTRC provides the space, staff, and equipment necessary to conduct a broad range of research procedures in children, including measurement of insulin sensitivity (insulin and glucose clamps, OGTT, IVGTT), body composition measurements, medication administration and infusions, bronchoscopies, fat and muscle biopsies, maximal and submaximal exercise tests, echocardiography for vascular and cardiac studies, measurement of total energy expenditure and rates of macronutrient utilization, and conduct short- and long-term exercise and dietary intervention studies, as well as specimen collection and processing. All procedures are supervised by highly-qualified and experienced personnel. All staff receive HIPAA and Good Clinical Practice training. Nurses are Pediatric and Basic Life Support (BLS) certified. Health technicians are BLS certified.

The CHCO CTRC has up to four inpatient beds located on the 9th floor of CHCO at the Anschutz Medical Campus and an adjacent wet lab for sample processing. The CTRC utilizes this space as needed and, if patient rooms are not being utilized, they are released for hospital use. Experienced research nursing and health technician support is available 24h/d, 4d/wk.

The CHCO outpatient CTRC consists of 5,973 sq ft of space located on the 3rd floor of the outpatient pavilion at CHCO which houses four infusion rooms, six exam rooms, an Echocardiography lab, one treatment room, two consult/consenting rooms, three staff workrooms, a secure medication room, and a wet lab for sample processing. The body composition (DXA) laboratory is located in the Radiology Department on the 1st floor. The CTRC clinical outpatient facility is generally open weekdays 7am – 6pm. During these hours, experienced nurse practitioner, research nursing, health technician, laboratory, and nutrition support is available. Outpatient visits that occur outside of regular opening hours are accommodated by request.

The CHCO CTRC facility has 7.1 FTE of research nurses, 1.0 FTE of health technician support, a 1.0 FTE sonographer (shared between UCH and CHCO CTRCs), 4.4 FTE of nutrition and metabolic kitchen staff, and 5.2 FTE of core laboratory staff support. This core of research professionals has extensive experience in conducting and documenting research for a diverse patient population from birth – 49 years of age, both healthy and with a range of diseases such as type 1 and type 2 diabetes, obesity, cystic fibrosis, cardiovascular disease, chronic hepatitis, rare genetic and metabolic diseases, gastrointestinal disease, cholestatic and fatty liver diseases, HIV, various forms of infectious diseases, etc.

Perinatal (PN) CTRC

Facility

The PN CTRC is a mobile nursing service located on the Anschutz Medical Campus to facilitate research in pregnant women and newborns, primarily at University of Colorado and Children's Hospital Colorado

Labor and Delivery (L&D) and Neonatal Intensive Care (NICU) units. This unit facilitates screening, consent, and enrollment of these vulnerable populations as well collecting and processing biological specimens for research. The PN CTRC has 480 sq ft of office and storage space on the 4th floor of the CHCO Administrative Pavilion, directly adjacent to the hospital, and wet lab space for sample processing adjacent to the UCH NICU, within the CHCO NICU, and in the basement of the East Tower at CHCO. All nurses have NICU experience. The PN CTRC is available 24h/7d with staff on call.

The PN CTRC has 4.0 FTE of research nurses and 1.0 FTE of health technician support. This group of professionals has experience conducting research in a broad range of newborns and pregnant women including premature infants and neonates with severe illnesses such as respiratory failure, respiratory distress syndrome, persistent pulmonary hypertension, cardiac disease and extreme prematurity, and pregnant women with pre-eclampsia, premature preterm rupture of membranes, gestational diabetes, obesity, and HIV.

National Jewish Health (NJH)
Facility
The NJH CTRC provides space, nursing services and core laboratory services for a broad range of research specializing in, but not limited to, Pulmonary, Asthma, Immunology and Allergy for adult and pediatric populations. The unit consists of 4 patient care exam rooms, 1 interview room, and 1 negative air flow room. Two rooms are equipped with oxygen flow meters. There are 593 square feet of dedicated space for patient care use located on the third floor of the Goodman Building and 873 square feet of office space. The unit is staffed by 1.5 RN's and is supported by a Nurse Practitioner and 1.0FTE of administration/regulatory support. History and Physical Exams, skin biopsies, consenting subjects for studies, spirometry, skin testing, induced sputum, sweat testing, medication administration, 12 Lead EKG, etc. are performed in the unit. The unit works with the Pharmacy for medication storage and distribution.

University of Colorado Boulder (CU-B)
Facility
The CU-B Clinical and Translational Research Center is the only active NIH-funded CTRC
Facility not located at a clinical institution in the U.S. It is an AAAHC-approved health care facility with 4,000 sq ft of dedicated CTRC space on the 3rd of the Wardenburg Health Center at the Boulder Campus. The facility includes 5 outpatient research protocol rooms (one is a Faraday cage which facilitates structured, not electrical, interference), an exercise testing/indirect calorimetry room, a body composition (DEXA) laboratory, a nutritional consultation room and a wet laboratory for processing blood and tissues. The CTRC has 1.25 FTE staff physician coverage (funded in the past by the Chancellor's Office at CU-Boulder), 3.0 FTE research nurse support, an Integrative Physiology Core Laboratory with 1.2 FTE personnel support, a 0.5 FTE bionutritionist, and a 1.0 FTE medical technician. There is an on-call nurse and physician available in the evenings 7 days/week to respond to research participant needs/concerns.

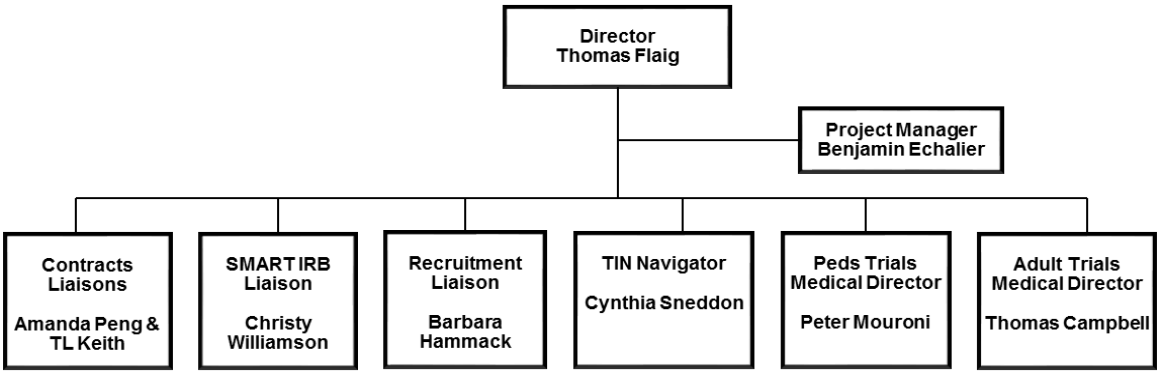
CTRC Core Laboratories
Facilities
CTRC Core Laboratories are located at UCH, CHCO, and NJH. The CHCO Core Laboratory is 10,000sq ft of space located in the basement of CHCO, adjacent to the hospital's clinical laboratory. The UCH Core Laboratory is 1,600 sq ft located within the UCH CTRC outpatient space on the third floor of the Leprino Building. The NJH Core Laboratory is 300 sq ft located in the Goodman Building. All laboratories are College of American Pathologists (CAP)- and Clinical Laboratory Improvement Amendments (CLIA)-accredited and provide trained personnel, reagents, equipment, and QC capabilities to conduct over 250 specialized assays for research (full list at http://www.ucdenver.edu/research/CCTSI/programs-services/ctrc/lab-services/Pages/Lab-Assays-Pricing.aspx). There is no redundancy in the services offered by the CCTSI Core Laboratory Network: the UCH Core lab specializes in hormone and metabolite assays (3.6FTE); CHCO Core Laboratory focuses on inflammation markers, fat-soluble vitamin measurement, specific protein and pulmonary fluid processing (5.2 FTE); and NJH Core lab specializes in flow cytometry, specialized cell culture, and DNA and RNA extraction (1.0 FTE).

CCTSI Bionutrition Core
Facilities

The CCTSI Bionutrition Core consists of two groups of professionals: 1) scientists and nutritionists with extensive experience in nutrition and metabolism research (2.3 FTE) and 2) food service staff trained to prepare and distribute weighed, metabolic meals from our commercial research kitchen (1.8 FTE). The commercial kitchen is located at the UCH CTRC outpatient facility with a smaller food preparation facility on the 12th floor CTRC at CHCO. The kitchen and all staff designing and preparing diets are ServeSafe certified. Meals are prepared, stored and shipped to CTRC sites for distribution as needed, and are provided on a fee-for-service basis. The CCTSI provides all of the necessary computers, software, office space, and other resources for providing: dietary intake assessment, both traditional and novel methods; measurement of hunger and satiety; growth, body composition, and indirect calorimetry; protocol-specific dietary counseling and instruction; development of study-specific educational materials; consultation on study design and ways to achieve specific dietary intervention targets; design, preparation, measurement, and dispensation of study-specific meals and foods; and design and product development for novel foods and diets (e.g. foods to mimic Agrarian dietary intake that are palatable to Americans, specific allergen-free food items and allergen-added counterparts with equivalent taste, volume, and texture for blinded studies, formulation development for palatable high fiber foods for long-term dietary intervention studies).

FACILITIES AND OTHER RESOURCES

NETWORK CAPACITY: THE TRIAL INNOVATION NETWORK (TIN) HUB LIAISON TEAM



The Trial Innovation Network (TIN) Hub Liaison Team encourages, supports, and promotes multi-center investigations, and provides an environment where NIH-supported clinical trials are conducted efficiently, compliantly, and with the highest quality. The team consists of the Hub PI, Director, Medical Directors for both adult and pediatric studies, a project manager, central IRB liaison, contracting liaison, recruitment facilitator, research navigator and an honest broker for recruitment. The TIN team will build on the strong clinical research structure currently in place to support clinical trials within the CCTSI and expand the opportunity to both propose multi-center trials via the TIN and recruit patients locally for TIN-sponsored trials. The TIN team has members that are imbedded in the same space as the Regulatory Knowledge and Support Core and the CCTSI office space, to facilitate collaboration, leverage existing expertise, and contribute to the overall goal of streamlining the startup and coordination of multi-site clinical trials.

The local TIN Liaison Team will include:

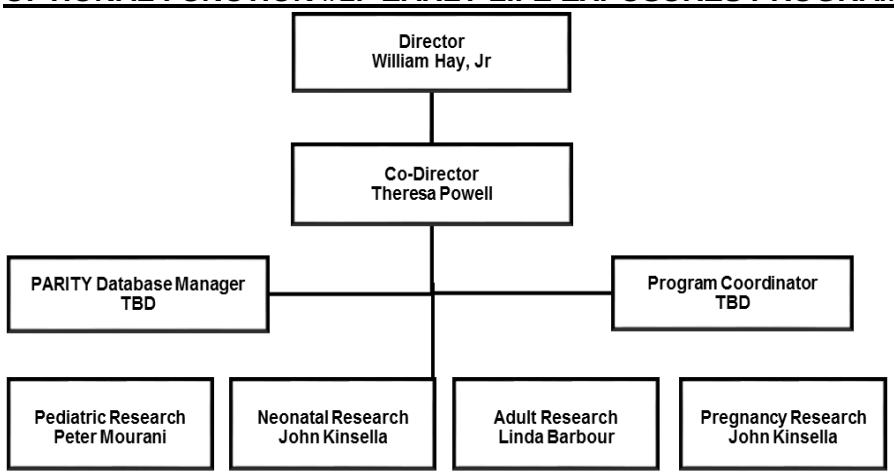
- Director – Thomas Flaig, MD
  Dr. Flaig, Professor of Medicine, is the Chief Clinical Research Officer for UCHealth and the Associate Dean for Clinical Research at the University of Colorado. Dr. Flaig is a Medical Oncologist with extensive experience in conducting clinical trials in the area of Genitourinary Cancers. He has been the local PI on more than 25 clinical trials, and also as the national PI on NCI/National Clinical Trial Network trials. He previously served in the University of Colorado NCI Comprehensive Cancer Center as the Cancer Clinical Trials Office Medical Director and subsequently as the Associate Director of Clinical Research. *He will be responsible for overall operations of the TIN, participation in conference calls and meetings, and communications with TICs and RICs and NCATS.*
- Medical Director (Adult health) – Thomas Campbell, MD
  Dr. Campbell, Professor of Medicine, Division of Infectious Diseases, also has served as Medical Director of the UCH CTRC since 2008. His research focus is the use of antiretroviral agents to treat and prevent HIV infection and AIDS-related complications. He is Site Leader for the UCH Clinical Research Site in the NIAID AIDS Clinical Trials Group (ACTG) and a member of the ACTG Executive Committee. He led the design, implementation, and dissemination of 3 NIH-funded international clinical trials from 2002-2016. He has served as the local PI for 52 ACTG and HIV Vaccine Trials Network clinical trials and 33 pharmaceutical industry clinical trials. Dr. Campbell served as a liaison for the establishment of new ACTG clinical trials sites in Zimbabwe and South Africa from 2003-2008. *He will be responsible for operations and implementation of adult clinical trials of the TIN.*
- Medical Director (Child health) – Peter Mourani, MD
  Dr. Mourani, Associate Professor of Pediatrics, is the Medical Director for the Children's Clinical Research Organization (CCRO) and works with investigators to optimize clinical research operations at CHCO in this capacity. He is also Director of Clinical Research in the Section of Pediatric Critical Care Medicine at CU SOM and Children's Hospital Colorado. Dr. Mourani's NIH-funded research focuses on the mechanisms of bronchopulmonary dysplasia and pulmonary hypertension in children. *He will be responsible for operations and implementation of child health clinical trials of the TIN.*
- TIN Project Manager – Benjamin Echalier, MS, MBA, CCRP
  Mr. Echalier is the manager of the CCTSI Research Coordinator team at CU-AMC and has worked to support regulatory submissions, data entry and other general coordination for clinical trials in multiple specialties. He has over 5 years of experience managing clinical research teams for both CROs and in the academic research environment. He was most recently a senior project manager for a large CRO

responsible for oversight of clinical trials for a variety of sponsors. *He will be responsible for project management and implementation of TIN protocols at our site.*

- Central IRB Liaison - Christy Williamson, CCRP
  Ms. Williamson is the Senior Facilitation Manager with the Clinical Research Support Center at UC Denver and has a strong background in clinical research and regulatory and IRB coordination. She has been an Education Consultant in the same group and has extensive experience working with multiple IRBs, including with the central IRB mechanism, throughout her career. *Her responsibilities will be to ensure timely and compliant IRB reliance agreements, facilitate use of central IRBs, and streamline local IRB processes for TIN studies.*
- Contracting Liaison - Amanda J. Peng, MS
  Ms. Peng has a Master's Degree in Health Science and Technology from the Massachusetts Institute of Technology and currently serves as the Senior Clinical Trial Contracts Manager at CU-D. She has worked as a clinical research associate in the UCSF Department of Orthopedics, was a Trainer and Team manager for the Clinical Trial division budget team at Stanford University, and is currently a Senior Clinical Research Contracts Manager at CU-Denver. She has a strong background in budgets, contracts, team management, process improvement, change management, institutional training, and identification of complex issues with attention on solution focused communication and problem solving. *Her responsibilities will be to facilitate timely and complete execution of contracts related to TIN studies.*
- Recruitment Facilitator - Barbara N. Hammack, Ph.D.
  Dr. Hammack has been the Research Subject Advocate (RSA) for the CCTSI since 2008. She has taught regulatory science and research ethics and is the director for an investigator focused clinical trials course. She has close connections and has organized multiple recruitment resources at UC Denver and nationally that put her in a strong position to facilitate recruitment at our site. *Her responsibilities will be to develop, implement and facilitate research participant recruitment and retention strategies in coordination with the RICs*.
- Research Navigator - Cynthia Sneddon MPH, CCRC
  Ms. Sneddon is a facilitator in the Clinical Research Support Center at UC Denver and provides one-on-one guidance to PIs and study teams with regards to regulatory areas, IRB submissions and other issues that need attention. She has an extensive clinical research background, with experience as a research coordinator, regulatory coordinator and IRB coordinator at UC Denver. *Her responsibilities will be to assist investigators and their teams in accessing and coordinating the various resources of the TIN, RICs, TICs and CCTSI in order to either submit a TIN request or be a local site PI for a TIN study..*
- Honest Broker for recruitment – TBA
  The Honest Broker will be a new position to facilitate the identification of subjects for clinical trials by working closely with the Health Data Compass team (our research data warehouse which includes patient data from UCHealth, CHCO and CU Medicine. This Honest Broker will work closely with investigators to identify and contact potential participants with whom the investigators do not have a treatment relationship.
- Clinical site operations coordinator
  - CHCO - Jeannine Duffield, BA, Director of Research Administration and Operations, CHCO Research Institute
  - UCHealth – Laurie Blumberg-Romero, MA, CRA, Director of Research Administration for UCHealth

FACILITIES AND OTHER RESOURCES

OPTIONAL FUNCTION #1: EARLY LIFE EXPOSURES PROGRAM (ELEP)



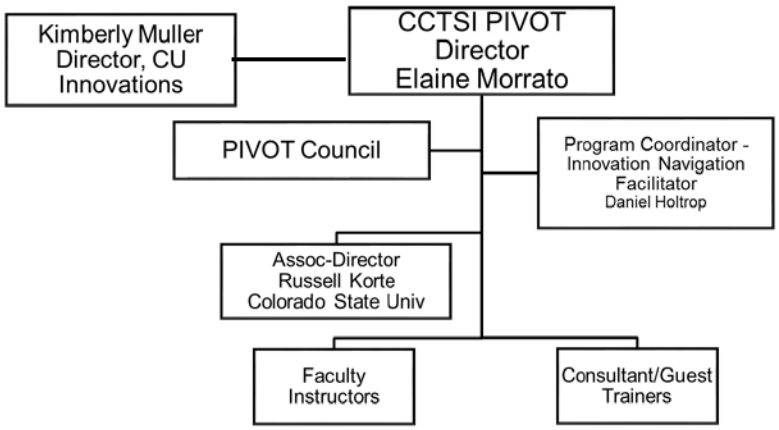
The overall goal of ELEP is to support and promote clinical and translational research in children of all ages, pregnant women, and the mother-child dyad to improve child health and prevent diseases, thus preempting adverse outcomes that increase disease burden and the cost of health care over the life span. ELEP provides specific support for multidisciplinary, integrated, translational research focused on health problems that begin early in life and during childhood. The research initiative in ELEP addresses the life trajectory of the mother and child, initiating new collaborations among basic, clinical, and translational scientists in multiple disciplines and for providing a streamlined infrastructure for longitudinal studies to accommodate lifespan research.

ELEP promotes research of the highest scientific and ethical quality in special populations by supporting investigator knowledge and training in the special regulatory protections in place for these populations, pre-reviewing protocols for scientific merit and insuring that adequate participant protections are specified, and providing information and resources for families considering study participation. ELEP investigators frequently use the Perinatal CTRC and CHCO CTRC facilities and resources in their research studies.

The ELEP Perinatal Research Facilitation Committee is a group of experienced perinatal investigators, research nurses, and coordinators who assist investigators working with pregnant women, preterm infants, and newborns. This committee assesses the feasibility of each protocol, identifies potential overlap with existing studies and, if so, facilitates sample sharing, fosters collaboration between investigators working in similar areas, and assures that investigators are aware of existing data and biobank resources that could aid their research. This committee is vital to promote collaboration, insure maximal utilization of rare and/or small samples (eg. from premature infants), and prevent competitive recruitment of vulnerable populations.

FACILITIES AND OTHER RESOURCES

Optional Module #2: Innovation Ecosystem (PIVOT)



Innovation Corps (I-Corps™) uses proven customer-discovery methodologies for startups. It was developed for academic researchers by serial entrepreneurs working with the National Science Foundation. I-Corps@CCTSI is a team-based short course designed for faculty, staff and students. The program guides teams through the early stages of customer discovery where they can test the business model hypotheses for their technology or idea to accelerate the translation of innovations from the lab to clinical practice. I-Corps@CCTSI leverages and partners with other entities which promote innovation such as the UCD Technology Transfer Office and the Children's Hospital Colorado Center for Innovation. These partnerships facilitate collaboration, access to a large knowledge base and investor pool, access to proof-of-concept funds, and interdisciplinary expertise.

PIVOT, CE&R, and TWD leverage the resources of ACCORDS. ACCORDS is a health services research organization which provides infrastructure support and expertise via a team of experienced research scientists in practice-based research, pragmatic clinical trial, health information technology, mixed-methods evaluation, data center management, and biostatistics. Scientific collaboration occurs among a team of scientists that work across disciplines and interests to form a vital and thriving scientific community. The mission of ACCORDS is to contribute to improving health, both locally and nationally, by conducting state-of-the-art outcomes and community translational research that will impact clinical practice and health policy and by developing researchers to further this work. To accomplish this mission, ACCORDS has developed expertise in four methodological "core" areas: 1) Qualitative Science; 2) Practice-based Research Networks (PBRNs); 3) Biostatistics and Analysis; and 4) Health Information Technology (HIT) and mobile health. Topic areas of particular strength in ACCORDS are primary care, obesity, cardiovascular disease, diabetes, cancer, asthma, depression, and surgical outcomes. ACCORDS is also organized along four interdependent programmatic areas: 1) Research (Adult and Child Programs and Dissemination/Implementation (D/I) Program; 2) Education; 3) Research Training Programs; 4) Community Engagement and Outreach.

EQUIPMENT: HUB RESEARCH CAPACITY

University of Colorado Hospital (UCH) CTRC

- Portable indirect calorimetry (IC): True Max 2400 and TrueOne 2400 Metabolic Measurement Systems (Parvo Medics, Sandy UT), Ultima CPX 5530 (Medgraphics Corp, Saint Paul, MN)
- Maximal and submaximal exercise testing: Corival Ergometer and Lodebike 906900 (Lode Holding Company, Groningen The Netherlands), Velotron Pro exercise bike (RacerMate Inc, Seattle WA)
- Body composition measurement (Dual X-ray Absorptiometer): Discovery W (Hologic, Marlborough, MA)
- Stress Testing: Quinton Q-Stress Cardiac Stress Testing System with treadmill (Mortara, Milwaukee WI)
- CSMi Humac Norm isokinetic dynamometer (Computer Sports Medicine Inc, Stoughton, MA)
- Whole Room Calorimeter: CO_2 Analyzer AO2000 System (ABB Inc, Wickliffe OH), differential O_2 Analyzer Sable FC-2, Oxygen Analyzer (Sable Systems, Las Vegas, NV), Oxymat 6 Gas Analyzer (Siemens, Washington DC)
- *Peripheral Quantitative Computed Tomography (pQCT):* Large Bore Scanner XCT 3000 (Orthometrix Inc, Naples FL)
- Cardiovascular Imaging: Ultrasound Vivid 7 and Vivid E9 (GE Healthcare, Pittsburgh PA)
- Cardiac Monitoring: M8004a Cardiac Monitoring System (Philips , Andover MA)
- Sample Processing: 3 x Algra 6r refrigerated centrifuges (Beckman Coulter, Brea CA)
- Bronchoscopes: 2 x Olympus Airway Mobile Scope MAF Type TM (Olympus America, Center Valley PA), and 2 x Pentax FB-18BS Bronchoscope (Montvale, NJ)

Children's Hospital Colorado (CHCO) CTRC

- Body composition measurement: DXA Discovery A (Hologic, Marlborough, MA), BodPod (COSMED, Concord CA)
- Exercise equipment: Treadmill F85 (Sole, USA), and Ergomatic 828 E (Monark, Vansbro Sweden)
- Sample processing: Allegra X-22R Centrifuge (Beckman Coulter, Brea CA), Allegra X-30R centrifuge (Beckman Coulter, Brea CA), and Heraeus Multifuge 3L-R Centrifuge (Thermo Electron Corporation, Madison WI)
- Sample storage: 60082 refrigerator (Kenmore, Brea CA), GIE21 refrigerator (GE Appliances, Pittsburgh PA), Fridge (U-Line), Freezer (Sanyo), FUF20 Freezer (GE Appliances, Pittsburgh PA)
- Cardiac monitoring: Mac 1200 ECG system (GE Healthcare, Pittsburgh PA)

Perinatal (PN) CTRC

- Body composition measurement: PEAPOD (COSMED, Concord CA)
- Sample storage: freezers ULT185-5-A33 and 8603 (Forma, Asheville, NC)
- Sample processing: Refrigerated benchtop centrifuges G032 (Beckman Coulter, Palto Alto, CA), and L017 (Beckman Coulter, Germany)

National Jewish Health (NJH)

- EKG machine: ELI380 (Mortara Instrument, Inc., Milwaukee, WI) and MAC5500 CLR STD ENG NA AHA, (GE Medical Systems Information Technologies, Wauwatosa, WI)

- Spirometry: 2 x MCG Diagnostics (Breeze Suite version 8.1) (Medgraphics Corp, Saint Paul, MN)

University of Colorado Boulder (CU-B)

- Cardiovascular Imaging: Xario XG multi-specialty ultrasound imaging system (Toshiba America Medical Systems, Inc., Tustin, CA) with high resolution (7.5 and 12 MHz) linear array transducers
- WinDaq data acquisition software (Dataq Instruments, Akron, OH)
- Vascular Imaging Acquisition and Analysis: Vascular Analysis Tools software version 5.10.9 (Medical Imaging Applications, LLC, Coralville, IA) equipped with Top Performance Analysis Integrated System with imager and frame grabber (DICOM, Rosslyn, VA), vascular ECG-gating module (University of Iowa, Iowa City, IA) and MIA Vascular Research Tools 5 analysis software
- Forearm Cuff Occlusion: E20 Inflator AG101 Air Source, Rapid Version Cuffs (Hokanson, Inc., Bellevue, WA)
- Infusion pumps for saline and vitamin C: Imed Gemini PC-2TX (Alaris Medical Systems, San Diego, CA)
- Arterial Blood Pressure and ECG: Recording system with pressure transducer and ECG amplifiers (Gould ACQ-16, Gould Instruments, Valley View, OH)
- Semi-Automated Resting Blood Pressure Measurements: Datascope Accutorr V (Mindray DS USA, Inc., Mahwah, NJ)
- Ankle-Brachial Index: Transcutaneous Doppler flowmeters 810-A, (Parks Medical, Aloha, OR)
- Body Composition Analysis: Lunar Prodigy Dual Energy X-ray Absorptiometry (DEXA) system and

encore analysis software version 15 (GE Medical Systems, Madison, WI)

- Nutritional Analysis: Nutrition Data System for Research (NDSR; Nutrition Coordinating Center, University of Minnesota)
- Exercise Testing: Ultima gas analyzer module with ECG interface (MedGraphics, Saint Paul, MN), BreezeSuite ventilatory data collection software version 7.2C (MedGraphics, Saint Paul, MN), Trackmaster 425 Treadmill and 12-lead ECG-treadmill interface (Full Vision Inc., Newton KS)

CTRC Core Laboratories

- Cold Sample Storage: Freezer Forma 923, Ultracold Forma 983, 4 x Ultracold Forma 995, 6 x Thermo Forma 8000 series , Thermo Electron, Forma 989 Dd , 2 x Panasonic -80C (Panasonic Healthcare Corporation of North America, Wood Dale IL), Forma Ultra 990, Undercounter 3.6ºC Isotemp (ThermoFisher Scientific, Waltham MA); Ultra 500BX (Sanyo, San Diego CA)
- Centrifuges: 6 x Allegra 6r, Allegra X-15R, Avanti 30, Avanti J-20 (Beckman Coulter, Brea CA); Sorvall Lengend RT and RT6000D, RC3B Plus (ThermoFisher Scientific, Waltham MA); 2 x Eppendorf 5702R (Westbury, NY), 2 x Centra CL3R (Thermo IEC, Waltham,MA); 2 x Thermo Electron Heraeus Multifuge 3L-R (Waltham, MA); Fisher Accuspin Micro 17, Fisher Marathon 16KM, and Eppendorf 5415C; Shandon Cytospin 3
- HPLC: ICS-3000 (Dionex , Sunnyvale CA), 2 x Waters 2487 (Waters, Milford MA), Detector For Hplc ELSD2000 (Alltech, Lexington, KY), 1 x Waters UPLC with Detector (Waters, Milford MA)
- Real-time Whole Blood/Plasma Chemistry: 2 x 2300D Glucose Lactate Analyzer (Yellow Springs Instruments; YSI, Yellow Springs OH), 3 x Glucose Analyzer GM9 (Analox

Technologies, Atlanta, GA); DCA Vantage Hemoglobin A1C analyzer (Siemans, Tarrytown, NY)
- Gama Counter: Wizard 1470 (PerkinElmer, Waltham MA)
- Spectrophotometers/Plate Readers: Multiskan Spectrum Thermo Lab Sys 1500, Biotek El-808, Biotek Synergy/HTX and ELx800 Plate Readers (Biotek, Winooski, Vermont), 2 x Beckman Coulter DU650 (Beckman Coulter, Brea CA), Nanodrop Tech ND-1000, Nanodrop One (ThermoFisher Scientific, Waltham MA), Spectro Flow Plus and infinite M200 PRO (Tecan US, Morrisville NC)
- Autosampling: Biolc AS (Dionex Corporation, Sunnyvale CA) Miniprep 60 Basic System, MP60 (Tecan US, Morrisville NC)
- Antek 9000 Series Elemental Nitrogen Analyzer (PAC, Houston TX)
- Chemistry Analyzers: Beckman AU480 and Access 2 (Beckman Coulter, Brea CA), 2 x Cobas Mira Plus (Roche, Indianapolis IN), Nephelometer Dade Behring (Siemens, Washington DC)
- Multiplex assays: BioPlex Luminex 100, Luminex 200, Luminex FLEXMAP 3D (Luminex Corporation, Austin TX), Aushon Circascan multiplex instrument (Aushon BioSystems, Inc, Billerica, MA)
- Electrophoresis System: Capillary electrophoresis system (Waters, Milford MA)
- Microscopes: Nikon Optiphoto and Nikon Eclipse E400 (Melville NY), 3 x Olympus (Olympus America, Center Valley PA)
- Immunoassays: Immulite 1000 Analyzer (Siemens, Washington DC); Liaison Chemiluninescence Analyzer (DiaSorin, Stillwater, MN), IDS iSYS Analyzer (Immunodiagnostics Systems, Scottsdale, AZ)
- PCR: Applied Biosys 7500, DNA Engine (BioRad)
- Automated Cell Counter: Invitrogen Countess (ThermoFisher Scientific, Waltham MA)

CCTSI Bionutrition Core
- Diet design software: ProNutra (Viocare Inc, Princeton NJ)
- Analysis of dietary intake: Nutrient data Systems for Research (NDS-R) software (Nutrition Coordinating Center, University of Minnesota)
- Portable indirect calorimetery (IC): Vmax Spectra-29N and Encore29 metabolic measurement systems (Sensormedics; Yorba Linda, CA)
- High Precision Balances (food weights and stable isotope additions): 5 x Ohaus Pro Scout SP4001, Ohaus Adventurer AX5202 (Ohaus Corporation; Parsippany, NJ), Mettler Toledo New Classic MF (Columbus, OH)
- Refrigeration/freezer storage at UCH inpatient CTRC and CHCO CTRC: T-35 double door refrigerator, T-46 double door refrigerator, T-23 single door freezer, and T-35F double door freezer (True Manufacturing Co; O'Fallon, MO), Manitowoc Freezer UD-140A (Manitowoc Refrigeration, Manitowoc, WI), UF21355 Freezer (Sunpentown International, City of Industry, CA)
- Diet preparation: full commercial kitchen including a walk-in freezer and refrigerator, a Vulcan Hart range, and Hobart commercial dishwasher.

EQUIPMENT: TRANSLATIONAL INFORMATICS
- 768 cores (Xeon E5-2680 v3 at 2.5Ghz), 4TB of RAM and 3.7 PB of useable storage
- Scheduler (SLURM), manager nodes, master nodes, login nodes, compute nodes, storage and cluster management software
- 3.7 PB of useable data storage

- Infiniband switches
- Redundant 10 gigabit Ethernet connectivity to OIT’s current network core
- Six servers running VMware vSphere virtualization: each server has a minimum of 36 Xeon v3 cores at 2.3Ghz and 256GB of RAM
- Fibre channel SAN: 30TB of solid state disk.
- Redundant 10 gigabit Ethernet connectivity to OIT’s current network core
- 36 Xeon v4 cores and 1.5 TB RAM