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CCTSI is supported in part by Colorado CTSA Grants UM1TR004399, T32TR004366, T32TR004367, K12TR004412 from the National Center for Advancing Transitional Science

Element C1: CTS Workforce Development

B1: What are the major goals of the project

The purpose of the CCTSI's Workforce Development (WD) is to develop, deliver, demonstrate and disseminate flexible, evidence-informed clinical and translational science and research (CTSR) WD programs (for all clinical research staff professionals [CRSP] and scientists, including T32 and K12 programs) to prepare and retain a highly qualified inter-disciplinary team-oriented workforce which embraces diversity, inclusion, and health equity (**DIHE). Our Goals** are:

Goal 1. Weave our value, **Diversity Accelerates Research and Translation,** into all WD programming.

Goal 2. Support tailored learning to address needs of CRSP and scientists for their ability to conduct rigorous and efficient cutting-edge CTSR by providing comprehensive educational programming.

Goal 3. Enhance the CCTSI's workforce effectiveness by providing **career development training** in Teaming and Leading, Mentoring, and Communicating Research.

Goal 4. Ensure the entire CCTSI workforce receives **comprehensive training** in Diversity, Inclusion and Health Equity in Research, Good Clinical Practice, Responsible Conduct of Research, research ethics, and regulatory compliance.

Goal 5. Achieve **beneficial impact of WD programming** using established metrics that are monitored and reviewed per program at least annually, by engaging with and listening to feedback from the Workforce, and by making necessary modifications for effective programming.

B2: Accomplishments

The table below includes the programs offered through Workforce Development along with a program description and activities this first year.

Workforce Development (WD) Program Portfolio	
Program (Goal(s) addressed)	**Description of Program**
For all Clinical Research Staff Professionals (CRSP), Researchers, Trainees and CCTSI T32 and K12 trainees	
Responsible Conduct of Research (RCR), Good Clinical Practice (GCP) (Goal 4)	Curriculum to develop competence for GCP, RCR, regulatory knowledge, rigor and reproducibility. Variety of training forums: courses, seminars, individual consults, online modules, webinars. Annual reach ≥1,600 attendees, 40 workshops and > 300 students/ year in graduate level ethics/RCR courses.
Diversity, Inclusion and Health Equity (**DIHE) NEW**, (Goals 1&4)	Working with CCTSI Community Engagement and Health Equity to develop an introductory level webmodule, workshops, and regular Community of Learning sessions. Topics covered: diversity in research, trust, community engagement and marketing research, cultural humility and competent communication, and study recruitment and retention. Working with CRSP leaders to integrate into their onboarding process and to embed Community of Learning sessions into their regularly scheduled meetings. CCTSI WD Director of DIHE is providing a 2-hour workshop to CCTSI T32 and K12 awardees.
Clinical Science Graduate Program (CLSC) (Goal 2)	Advanced CTSR training. > 40 courses: study designs, study/grant operations and conduct, ethics/RCR/GCP, grant writing, rigor & reproducibility. Enrollment: 110 degree-seeking students- including 20% CRSP staff, 77% clinicians. >150 non-degree students take courses/year; 40-50% are CRSP. New course: *Design and Conduct of Successful Rare Disease Clinical Trials* is being developed by Dr Taylor, MD PhD. A survey was conducted to identify key topics, format preferences and potential speakers/facilitators.

Dissemination and Implementation (D&I) **Certificate** in CLSC **NEW** (Goal 2)	Prepares graduates with D&I skills to design & conduct rigorous & innovative translational research. 12 credit hours completed through synchronous online learning. 15-20 students/cohort, approximately 30% out of state
Effectively **Communicating Research** to the Public **NEW** (Goal 3)	Three-part 1.5 hr workshop series provides an overview of how to engage the public - everyone from TV reporters to neighbors - and the world on social media. Each workshop will include hands-on practice and accompanying web module. Program pilot started in 2022. This year leadership of program changed to a Co-Director model with a communications specialist and CTSR investigator sharing the directorship. Offered program 3 times with "sell out crowds", maximum capacity reached. All CCTSI T32 awardees completed the program.
Leading and Teaming in Clinical Translational Science and Research **NEW** (Goal 3)	This program is led by our CSU partners. The original team science program is being revised this year to incorporate and integrate leading and teaming. The purpose is to build capacity to participate in and lead effective, interdisciplinary, translational teams. Topics include building relationships, diversity on teams and harnessing its power, conflict resolution, negotiation, leadership for all team members, collaborative knowledge creation, setting expectations, meeting management. This year, based on feedback, we returned to offering in-person workshops in addition to Zoom workshops, are adding/integrating leading topics, reducing redundancy and time required, and making introductory webmodule available off program's webpage. CCTSI T32 awardees participated in workshops.
ATLAS.Ti Webmodules	Workshops were turned into self-paced web modules using CU e-learning platform. 82 online learners.
For Clinical Research Staff Professionals (CRSP)	
CTSA Clinical Training Program (Goals 2 & 4)	Ongoing training in competencies tailored to CRSP needs. Two to four lunchtime modules are offered per month- each topic is repeated 3-4 times/yr: responsible conduct of research, informed consent, COMIRB beginner training, introduction to INfoEd (IRB portal), measurement of vitals and anthropometrics, recruitment and retention of study participants.
Clinical Research Staff Professional Development Program NEW (Goals 1-4)	Two leaders of the CRSP were identified and integrated into the monthly WD Leadership Advisory Council and Lisa meets with them monthly. *Monitor, Track, Report*: A survey was completed to identify needs of the community of CRSPs to assist with future programming. Monthly *Clinical Research Connections* are held to review new regulations, standards, and resources such as template forms, SOPs and checklists. An exciting initiative is developing an CRSP Onboarding Curriculum and Program that would occur over the first year in the position. *Preceptoring Summer Undergraduate Students:* In Summer 2024, there will be four undergraduate students from historically disadvantaged populations completing an 8-week preceptorship to introduce them to clinical research and careers as a CRSP. We are hoping that this becomes a source of recruitment for CRSP new hires. The CRSPs that will be serving as preceptors will be completing a mentoring across differences workshop prior to working with/mentoring students. *CTSA Hub Engagement* to increase CRSP relationships with other CTSA hubs our two lead CRSPs are now attending the monthly meetings, are part of the special interest group and will be attending the ACTS Translational Science 2024 conference. Our two CRSP leads have already benefitted tremendously from this engagement. These groups shared resources, best practices and provided important guidance and a sense of community.
For Researchers and Trainees (Required elements for CCTSI T32 and K12 trainees)	
CO-Mentor- mentor-mentee dyads (Goal 3)	20 hours of training for mentor-mentee dyads over a year. Attended by 60 mentors-mentees/year. Targets K awardees and new faculty and their mentors. All CCTSI K awardees and their mentors complete the program.
Mentoring^3: Mentee, Mentor and Peer NEW (Goal 3)	Program developed this year and involves 10-12 hours of workshop time supplemented by homework activities. Attended by mentees and mentors separately and as dyads. Based on CO-Mentor and Wisconsin's CIMER. Mentoring across differences will be discussed and supported by WD

	DIHE Director. The program is being piloted with the CCTSI T32 awardees and their mentors. Based on evaluations, it will be determined if and what modifications/revisions are needed. It will subsequently be open to pre- and post-doctoral trainees and their mentors.
Grant Review & Mock Study Sections- Pre F **NEW** along with Pre K and Pre R programs	3 programs to support development and submission of competitive grants for pre- and post-doctoral awards, career development awards and research grants. Programs involve 1) "How to prepare your grant" workshop; 2) Submit specific aims page reviewed by program faculty with applicant feedback; 3) Submit full grant; 4) Grant reviewed by 2-3 reviewers with written feedback; 5) attendance at mock study section to hear all reviews, discuss and pose questions; 6) Meet with faculty for feedback. Pre K: 44 letters of intent submitted; 35 full applications reviewed; 83 interdisciplinary reviewers. Pre R: 23 letters of intent submitted; 16 full applications reviewed; 47 interdisciplinary reviewers. Pre-F program was integrated into the CCTSI (webpages created, submission and review platform built out, and co-directors attend monthly WD Leadership Advisory Council). 76 pre-/post-doctoral trainees attended workshop; 68 full grant applications review; 51 interdisciplinary reviewers.
In support of Goal 5, all programs are evaluated by the CCTSI evaluation team. Annually programs are reviewed by members of the WD Leadership Advisory Council.	

B4: What opportunities for training and professional development has the project provided?

During the WD Leadership Advisory Council meetings, all committee members (program leaders and partners) receive professional development at four of our monthly meetings. The majority of our topics focused on supporting Goal 1- Diversity Accelerates Research and Translation and included workshops on mentoring across differences, the SCOTUS ruling and its impact, and increasing diversity in research. We also had a workshop on evaluating our programs and the Translational Science Benefits Model provided by Goldie Komaie PhD, CCTSI Evaluation lead.

B5: How have the results been disseminated to communities of interest?

Nothing to Report

B: What do you plan to do during the next reporting period to accomplish your goals?

- Develop and implement Diversity, Inclusion and Health Equity in Research modules and workshops into Clinical Research Professional onboarding curriculum
- Quarterly Communities of Practice meetings with ALL Clinical Research Professionals will be held regarding Diversity, Inclusion and Health Equity in Research
- To improve awareness of career options as a Clinical Research Professional, 3-4 undergraduate students will be mentored through summer internships by clinical research coordinators.
- All RCR workshops (not course based) will use standardized evaluations to inform the need and type of revision and overall satisfaction and usefulness of workshops that are attended by about 1,000 people/year
- Develop an additional course offered through the Clinical Science Program: *Design and Conduct of Successful Rare Disease Clinical Trials (Matthew Taylor, MD, PhD)*
- Revise the newly developed Mentoring^3: Mentors, Mentees, Peers program based on evaluation of pilot offering. Broader dissemination of the newly developed Mentoring^3: Mentors, Mentee, Peers to all T32 programs. Develop and pilot train the trainer type of program to increase the number of program faculty for Mentoring^3
- Effectively Communicating your Research to the Public program will be revising/restructuring format by moving to flipped classroom. Learners will complete webmodules prior to workshop to permit 100% experiential learning at workshops
- Add an additional faculty member to the Pre-K program specializing in dissemination and implementation research
- Work to publish experiences with our program, Effectively Communicating your Research to the Public.

- Continue to offer and revise/improve our programs through ongoing evaluation.

C2: Website(s) or other internet site(s)

Nothing to Report

C3: Technologies or techniques

Nothing to Report

E2: What is the impact on physical, institutional, or information resources that form infrastructure?

Several of our training and career development programs were developed and are provided to meet the needs and address the gaps identified by our partners and communities. For instance, Clinical Research Professional leaders were integrated into the WD core to improve integration and co-development of programs to meet the needs of Clinical Research Professionals, such as an onboarding program and weaving diversity into our research teams, conduct and study participants. Mentoring[3]: Mentors, Mentees, Peers was developed, and its provision expanded to meet the needs of other T32 programs and pre-doctoral programs.

Element C2: Community Engagement & Health Equity (CEHE) Core

B1: What are the major goals of the project

Goal 1: Develop the capacity of investigators and research staff to equitably engage diverse communities and stakeholders in clinical and translational research.

Goal 2: Develop the capacity of communities and stakeholders to equitably engage with research investigators and staff in clinical and translational research.

Goal 3: Continue to establish, build and maintain trust with communities and stakeholders through return of results to, interpretation and dissemination of results in partnership with communities and stakeholders.

Goal 4: Continuously evaluate and improve our capacity development activity on campus and in communities by measuring and monitoring our impacts on equitable engagement and involvement with diverse communities and stakeholders in clinical and translational research.

B2: Accomplishments (9/15/23-Present)

Goal 1: Develop the capacity of investigators and research staff to equitably engage diverse communities and stakeholders in clinical and translational research.

We continue to pursue **transforming our institutional environment** into one that supports and values community engagement in the research enterprise. The CE Core is an active member of the CCTSI Education and Training Core, and we have also worked with our grants and contracts office to promote and normalize administrative structures, such as our partnership with the Trailhead Institute, that allow us to more efficiently engage in contractual relationships with our community partners and have also allowed us to be more responsive and agile in the face of new collaborative opportunities.

Additionally, we are engaged in discussions with leadership from the Office of Diversity, Equity, Inclusion and Community Engagement to align efforts and to provide training opportunities for CCTSI faculty and staff. We now have two community representatives, one elected member of the **Partnership of Academicians and Communities for Translation (PACT) and one Community Research Liaison (CRL),** participating on the CCTSI Executive Committee. The PACT has become firmly entrenched within our CTSA as the nexus of the CEHE Core. The Council of 7 academic researchers and 7 community members has expressed continued commitment to our work and a renewed enthusiasm for what lies ahead. The PACT Council made significant strides this year, adding all CRLs as voting members of the PACT and working to more intentionally direct our efforts around health equity, commensurate with the addition of Health Equity to the name of our core.

At its Fall 2023 retreat, the PACT approved the following statement on Health Equity:

> Health is a fundamental human right. Health equity requires removing obstacles so that every person has the opportunity to attain their full potential for health and well-being.
>
> The Partnership of Academicians and Communities for Translation (PACT)* is working towards health equity by partnering with community to design, implement, and fund research, education, training and programs that support health for all people, in particular efforts focused on improving health outcomes experienced by people who are marginalized, disadvantaged, or underserved.
>
> Specifically, PACT is committed to:
> - Research that equitably benefits communities.
> - Mutual learning between community and researchers.
> - Supporting a research infrastructure that fosters equitable, long term community engagement.
> - Community based decision making.
> - The ethical and responsible collection, interpretation, storage, management, and sharing of data.

- Serving as thought partners and consultants for organizations that are exploring their own commitment to community engaged research and health equity.
- We will continue to evaluate internal processes to sustain efforts and ensure our actions equitably benefit community

** The Partnership of Academicians and Communities for Translation (PACT) is a partnership of researchers and community members working together to support and facilitate community-based participatory research (CBPR), build trust and connections between researchers and communities, and encourage institutional changes that allow all communities to benefit from health research.*

Colorado Immersion Training in Community Engagement (CIT) - A primary focus for the CE Core is to provide a clear pathway for investigators who are interested in community engaged translational research. This pathway is structured to provide education, training, funding opportunities, introduction into diverse communities, and ongoing coaching and mentoring for investigators and community-academic partnerships. The pathway begins with our Colorado Immersion Training in Community Engagement (CIT). The CIT offers researchers and students experiential learning opportunities related to Community-based Participatory Research (CBPR). The program occurs annually on campus and in alternating community settings: urban African American, urban Asian and Refugee, urban Latino, urban American Indian/Alaska Native (AIAN), rural northeast Colorado, and rural San Luis Valley. In 2023, we piloted a combined track focused on intersectionality in six urban underrepresented communities. We were able to accept 7 participants from a variety of research disciplines. The CEHE Core staff and Community Research Liaisons (CRLs) provide six months of follow-up mentoring and ongoing technical assistance for CIT participants to assist them in further developing their partnerships, developing shared research interests and identifying funding opportunities. Community-academic partnerships resulting from CIT have yielded multiple grant awards over eight cohorts. CIT participants have successfully acquired CCTSI pilot awards along with federal funding and money from PCORI. To date, 120 researchers have participated in CIT and each of them expressed the transformational nature of the experience in their program evaluations. We are currently planning for our 2024 CIT Cohort, which is scheduled to begin in May 2024.

Community Research Liaisons - Our Community Research Liaison program, a cornerstone of the CEHE Core, continues to thrive and has garnered national attention. We have worked closely with the Evaluation Center to better track CRL activities such as qualitative and quantitative data on the individuals and organizations they work with, and partnerships they are working to develop. Through the enhanced evaluation, CRLs also provide information on the progress of other CCTSI Community Engagement programs they are involved in, such as grant reviewers, trainers, and coaches with Pilot Grant awardees; work on various committees such as Education & Training and the Consults & Ethics Committee; and activities associated with the Colorado Immersion Training. CRLs are also able to share narratives of their experiences, success, challenges, and lessons learned in relation to the work they are carrying out on a monthly basis. We are currently exploring innovative reporting modalities utilizing social media to share real-time community-based activities and information.

Community Engagement Consults - We routinely provide Community Engagement Consults to investigators and study teams to assist them in improving their community engagement, recruitment and dissemination efforts. PACT members and CRLs participate as consultants. Our Community Consults team, in partnership with our team of CRLs and PACT Council, is also poised to serve as a critical link in the workforce development pipeline, offering technical assistance and mentoring to graduates of the Colorado Immersion Training in Community Engagement (CIT) program who are seeking grant funds to continue to grow community-academic research partnerships developed during the program.

We have made efforts to more closely connect to the Clinical Research Operations & Services recruitment center and the Office of Diversity, Equity, Inclusion and Community Engagement, which are referring appropriate protocols to Community Engagement. This partnership has resulted in an increase in consult requests to more than one per week during the grant period. We have re-convened a standing committee of

the PACT to accommodate the increased demand and are establishing processes to refer appropriate protocols to our **Community Clinical Trials Advisory Board**.

Goal 2: Develop the capacity of communities and stakeholders to equitably engage with research investigators and staff in clinical and translational research.

CO-CEAL - One of our continued collective achievements is our implementation of the CO-CEAL program. Our CCTSI CEHE Core received funding from NIH in May 2021 to join 20 CEAL Teams across the country in an effort to provide trustworthy, science-based information through active community engagement and outreach to the people hardest-hit by the COVID-19 pandemic, with the goal of building long-lasting partnerships as well as improving diversity and inclusion in clinical trials. We are now in our third year of funding, working with 5 racial/ethnic communities in Colorado to address health disparities. Our approach of using community data collectors for our surveys has resulted in an over 60% retention rate over 3 survey waves.

CO-CEAL Program Aims

- Identify promising engagement and outreach practices that communicate trustworthy, science-based information to communities experiencing health disparities.
- Evaluate effectiveness of community-specific messaging and materials delivered through trusted channels to address community-identified health concerns for adults and children in disproportionately impacted racial and ethnic communities.
- Understand partner network connections to the most vulnerable populations across the state, including gaps/weaknesses.
- Create a Community Clinical Trials Advisory Board to enhance collaboration between community-based organizations and clinical trial study teams and provide consultation with trial teams on community engagement.

We submitted a $5.4 million renewal application to NHLBI in February, 2024 to continue the CO-CEAL program for another four years, which was successfully funded. We also recently held our Convening Across Sectors for Colorado's Health Equity and Wellness (CASCHEW) conference, where we brought our CO-CEAL community and academic partners together in partnership with other CU departments to share information and resources.

Research Readiness - The CEHE Core over the last decade has developed a series of trainings, educational activities and funding opportunities to build capacity in community-academic research partnerships. These trainings are now being combined into a comprehensive Research Readiness training program to equip Community Based Organizations with the knowledge and tools to design their own organizational strategies and policies related to research and to effectively and equitably partner with researchers in all phases of the research process. Development and formalization of the Research Readiness program is ongoing. We have scheduled a pilot with a local CBO, Village Exchange Center, which began in March 2024.

Community Engagement Forum - We have partnered with ACCORDS to host a quarterly campus Community Engagement Forum designed to engage researchers and community members in discussions about Community Based Participatory Research in action. To date, we have hosted nine Community Engagement forums with 643 attendees. The Forum has also attracted a national audience with attendees from outside Colorado at each event. Additional CEHE Education and Training activities are listed below in section B4.

Goal 3: Continue to establish, build and maintain trust with communities and stakeholders through return of results to, interpretation and dissemination of results in partnership with communities and stakeholders.

iHeard CO - As part of CO-CEAL, we are working to understand and address the spread of health misinformation and disinformation in communities by conducting weekly surveys of community members in participating regions. This initiative, iHeard Colorado, helps to build knowledge in communities about the health-related topics being surveyed. Working with our CO-CEAL community connectors, we recruited a panel

of 200 community members in three regions (Denver Metro, San Luis Valley, Pueblo) who answer weekly surveys. Additionally, we recruited 20 Trusted Community Messengers to help disseminate survey results in the community. Survey response rates are as high as 86%.

Goal 4: Continuously evaluate and improve our capacity development activity on campus and in communities by measuring and monitoring our impacts on equitable engagement and involvement with diverse communities and stakeholders in clinical and translational research.

All of the CEHE Core's projects, programs and services are designed to achieve our Core's overarching objectives: a) Support and strengthen strategic community-academic partnerships to facilitate quality community-engaged research; b) Improve the institutional environment to support community engaged research; c) Facilitate the translation and dissemination of scientific discoveries into practical, community-relevant language and interventions; d) Strengthen the bidirectional links between the academic medical center, healthcare providers, and community members; and e) Infuse community engagement throughout the translational research spectrum.

The CEHE Core has continued to evaluate and improve our core programs. The Core's flagship programs, projects and services include: our Partnership of Academicians and Communities for Translation (PACT); the Community Research Liaison program; the Colorado Immersion Training in Community Engagement; the Improving Research through Community-Academic Partnerships pilot grant program; our annual PACT retreat; and multiple training programs for investigators, community members, and community-based organizations. Additionally, we are working to develop a comprehensive Research Readiness Certification Program for community-based organizations. Our Community Engagement Consultation Service is assisting investigators in planning and conducting research. We have worked with organizations locally and across the country to transform evidence-based recommendations into language and programs that are accessible to diverse communities using Boot Camp Translation. In addition to operating programs, we have made concerted efforts to disseminate what we've learned, presenting for numerous local, state and national audiences. We have also reached out to partner with other CTSA's across the country to apply our knowledge and experience in community engagement and have collaborated with several CTSA's on various grants and projects. A paper summarizing our CIT program is in its final draft stage. Finally, we have engaged more than 100 community partners in implementing the Colorado Community Engagement Alliance Against Health Disparities (CO-CEAL), which is described in detail below.

B4: What opportunities for training and professional development has the project provided?

- Let's Get Started - Introduction to CBPR for partnership development pilot awardees
- Let's Keep it Going – Training for joint pilot awardees
- Community Research Consultation Service
- Community Research Liaison Coaching and Mentoring
- Community Engagement training for Public Health Agencies
- Quarterly Community Engagement Forums
- Facilitation Training for Community Partners
- BCT Facilitator Training for Community Partners

B5: How have the results been disseminated to communities of interest?

Our primary method of community information dissemination is our CEHE website, along with our trusted community partners. Additionally, we published the following manuscripts and abstracts:

- *Sarah E. Brewer, Mary Fisher, Linda Zittleman, Meredith K. Warman, Meredith Fort, Emma Gilchrist, Jameel Mallory, Rebecca Mullen, Jose Barron, Amanda Skendadore, Farduus Y. Ahmed, Crystal LoudHawk-Hedgepeth, Montelle Tamez, Bethany M. Kwan, and Donald E. Nease,2024:* ***Rapid Community Translation in the Colorado CEAL (CO-CEAL) Program: Transcreating Messaging to Promote COVID-19 Vaccination****. American Journal of Public Health* ***114****, S50_S54,* ***https://doi.org/10.2105/AJPH.2023.307456****).*
- *Rivera Gordon K, Taméz M, Fisher, M, and Nease D. Community Engagement, One Mile High: Developing a pipeline for training in community-based participatory research for investigators in Colorado. Poster presented at the Association for Clinical and Translational Science conference, Washington DC, April 2023.*

- *Taméz M, Sweitzer E, Gordon K, Fisher, M, Nease DE. Colorado Immersion Training: Ten years of lessons learned and accomplishments. Poster presented at the Association for Clinical and Translational Science conference, Washington DC, April 2023.*
- *Rivera Gordon K, Taméz M, Fisher, M, and Nease DE. Community Engagement Forum: Sharing best practices in community-engaged research. Poster presented at the Association for Clinical and Translational Science conference, Washington DC, April 2023.*
- *Amanda Skenadore, MPH, Meredith Fort, PhD, MPH and Crystal LoudHawk-Hedgepeth, MSCS, MEd. 5004.0 - A community-focused COVID-19 vaccine health promotion campaign: Lessons from the community translation experience with the Denver urban American Indian/Alaska Native (AIANs) COVID-19 workgroup from 2021-2023. Oral presentation at the American Public Health Association Annual Meeting, Atlanta, GA, November, 2023.*

We also began working on creating a CEHE annual report and co-authoring two manuscripts with our community partners: one on the Community Immersion Training program and another on outcomes from our Community Research Liaison program. Both are still under development.

B: What do you plan to do during the next reporting period to accomplish your goals?

- During grant years 1-3 years a focus on implementation of programs described in Strategic Goals 1 and 2 with continuous formative evaluation of the implementation.
- During grant years 4-7 we will shift our focus from implementation to Strategic Goals 3 and 4 with a focus on continuing to develop relationships with our partner communities and stakeholders while continuously monitoring and improving our processes and outcomes on enrollment in clinical and translational research studies.
- Assess whether participants in clinical trials whose investigators and staff have participated in our trainings are more likely to match the demographics of Colorado or exceed representation of disproportionately impacted racial, ethnic and rural populations when trials address conditions where significant health disparities exist.

Goal 1: Develop the capacity of investigators and research staff to equitably engage diverse communities and stakeholders in clinical and translational research.

- Develop and provide training for research coordinators and staff in Community Engagement. Currently working with Clinical Research Operations and Services (CROS) Clinical Research Recruitment Program to plan workshops, trainings and other collaborative efforts. Working with ODICE on joint training/consult plans.
- Expand the capacity of our existing programs for training investigators in Community Engagement. New CIT Director leading effort to create a CIT certificate program. Currently partnering on the first Latino Health Certificate CIT experience with the Colorado School of Public Health.
- Expand the reach of the Community Clinical Trials Advisory Board (CCTAB) beyond COVID-19 related trials. CCTAB will actively advertise their consult services throughout campus.

Goal 2: Develop the capacity of communities and stakeholders to equitably engage with research investigators and staff in clinical and translational research.

- Continue the development and implementation of programs to train Community Based Organizations in research fundamentals. (Disseminate Research Readiness) RR pilot beginning in March with Village Exchange Center.
- Continue the development and implementation of programs to train individual community members to partner in the development and conduct of research in community settings (expand Community Connector model) Community Connector model will be refined, evaluated and expanded in future CO-CEAL efforts. iHeard project has secured additional funding – training will be provided to Trusted Local Messengers on dissemination of accurate health information and identification of health misinformation/disinformation.

Goal 3: Continue to establish, build and maintain trust with communities and stakeholders through return of results to, interpretation and dissemination of results in partnership with communities and stakeholders.

- We will continue to build out our public-facing CO-CEAL data dashboard
- We will continue to contribute to iHeard public dashboard

- We are actively working with CO-CEAL data collectors and community connectors to interpret and disseminate community survey data
- We are working in partnership with our CRLs and elected PACT members to develop two manuscripts with a community partner acting as the lead author on one manuscript.

Goal 4: Continuously evaluate and improve our capacity development activity on campus and in communities by measuring and monitoring our impacts on equitable engagement and involvement with diverse communities and stakeholders in clinical and translational research.

- Undergoing a strategic planning process with the PACT, working within our definition of Health Equity and our grant objectives to develop strategic milestones and benchmarks for the next 7 years.
- CRL payments and scopes of work have been restructured to be more equitable.
- CRLs all have a vote on the PACT Council.
- Currently revising PACT rules of operation to reflect a more participatory, equitable approach.
- CEHE annual report under development.

C2: Website(s) or other internet site(s)

- https://cctsi.cuanschutz.edu/community
- https://cctsi.cuanschutz.edu/community/co-ceal
- https://cctsi.cuanschutz.edu/community/iheard
- https://co.iheard.org

C3: Technologies or techniques

- Rapid Boot Camp Translation: *(Sarah E. Brewer, Mary Fisher, Linda Zittleman, Meredith K. Warman, Meredith Fort, Emma Gilchrist, Jameel Mallory, Rebecca Mullen, Jose Barron, Amanda Skendadore, Farduus Y. Ahmed, Crystal LoudHawk-Hedgepeth, Montelle Tamez, Bethany M. Kwan, and Donald E. Nease,2024:* ***Rapid Community Translation in the Colorado CEAL (CO-CEAL) Program: Transcreating Messaging to Promote COVID-19 Vaccination****. American Journal of Public Health* ***114****, S50_S54,* ***https://doi.org/10.2105/AJPH.2023.307456****).*

E2: What is the impact on physical, institutional, or information resources that form infrastructure?

The CEHE Core has become a core component of the CCTSI and University research enterprise, providing a long-term infrastructure for community engagement education, training and technical assistance and community engaged research initiatives. We have worked across programs and departments to assist investigators in establishing relationships in communities and leveraged our long-standing relationships to improve community engagement and research efforts across our campus and nationally among other CTSAs**.**

Element D1, Resources and Services

B1: What are the major goals of the project

Goal 1: Provide supervisory oversight of Resources & Services (R&S) operations
Goal 2: Develop expertise and capacity to support the design of virtual and real-world clinical trials
Goal 3: Accelerate start-up and completion of clinical and translational research studies
Goal 4: Ensure that R&S operations can respond to urgent public health emergencies
Goal 5: Enhance recruitment and retention of diverse research participants

B2: Accomplishments

Goal 1: Provide supervisory oversight of R&S operations

1.1 Supervisory oversight of R&S operations. The CCTSI supported supervisory and administrative leadership for key components of R&S to ensure 1) the safety, quality, and effectiveness of operations and 2) the training and competency of staff members who deliver services. This included the CTRC Network (nurse managers, medical directors), CTRC Core labs (directors), Nutrition and Exercise Core (director), and Cardiovascular Imaging Core (medical directors). These resources supported 252 adult and 145 pediatric clinical research protocols that had 14,756 and 3,260 study visits, respectively. The NJH and CU Boulder CTRCs accommodated 604 and 333 visits, respectively. The Nutrition Core dispensed 3,389 meals and provided 4,298 service hours; the Energy Balance Lab conducted 1,877 DXA measurements and performed 302 exercise tests; the Cardiovascular Imaging Core provided 423 service hours; and the CTRC Core labs performed 78,643 assays. Other components of R&S have been integrated into campus-wide services, but CCTSI support helps to ensure equitable access to services by early career and URM investigators. An example of this is the Biostatistics, Epidemiology, and Research Design (BERD) Core, which is a component of the CU Center for Innovative Design and Analysis (CIDA). CCTSI funding for the BERD supported 277 investigator requests for protocol development, with 28% from junior investigators and trainees. A major oversight accomplishment was the creation of the CU Biostatistics and Bioinformatics Ecosystem. This is an umbrella navigation system that includes five major biostatistics units (including the BERD) and the Cancer Center Bioinformatics Core. The launch occurred in April 2024, with an overarching goal of creating the right analytic teams in a timely manner for an investigator.

1.2 Natural Animal Models Core to develop guidance for veterinary multi-center trials, best practices for veterinary regulatory compliance and bio-archive management, and promote advocacy, training, and communication efforts. Dr. Tracy Webb transitioned to a faculty role to serve as Veterinary Clinical Trials Coordinator in the Department of Clinical Sciences. Activities in this role have included 1) regulatory support for 25 clinical research protocols, 2) template development of tools for clinical trials, and 3) creation of a training module on best regulatory practices in veterinary clinical trials (in collaboration with Dr. Cheryl London at Tufts University), which bridges a current gap in available veterinary clinical research training. The modules are being incorporated into recommended and required veterinary research team training at CSU and other institutions and are requirements for a new CTSA One Health Alliance (COHA) DVM/PhD Clinical and Translational Scientist Certificate program.

1.3 Dissemination of information about current and new R&S. Information on R&S available through the CCTSI was disseminated through various CCTSI email communications, town halls at CU-AMC and partnering institutions, and CCTSI stories published across the CU system. Additional communiques to extend the reach of R&S included staff newsletters, communications to CTRC users (including PIs, co-Is, and research coordinators), and numerous announcements for training opportunities, CCTSI events, and success stories.

Goal 2: Develop expertise and capacity to support the planning of virtual and real-world clinical trials

2.1 Pragmatic Trials Navigation Service. This service completed a preliminary environmental scan for the annual resource cataloging effort, created and tested a form to collect relevant info about pragmatic research resources, and engaged the Virtual Clinical Trials (VCT) core around opportunities for collaboration.

2.2 Establish a Virtual Clinical Trials Core. The VCT core is a component of the Decentralized Clinical Trials Program in the Office of Clinical Research Operations and Services in the VCR office. Progress in Year 1 included establishing a VCT working group that meets quarterly, providing language and support for ARPA-H submissions, and supporting new initiatives with CU Innovations. Additionally, the first meeting of the VCT

Community of Practice was held in February 2024. The VCT team has been coordinating with the Element E PEET program to plan for integration of PEET resources into the DCT toolbox as they are developed.

2.3 D&I Research Core services. The D&I Research Core conducted 11 free consultations, with 7 advancing to fee-for-service contracts, and developed SOPs and implemented iLab to track effort and invoice clients. The Core also developed the CCTSI Dissemination Product Library, which is a visual repository aiming to inspire and provide guidance for CCTSI investigators in crafting their own dissemination materials.

Goal 3: Accelerate start-up and completion of clinical and translational research studies

3.1 Study Start-up. The BERD (discussed above), D&I Research Core (discussed above), Research Studio program, Trial Innovation Network (TIN) Liaison Team, and CTRC Core Labs all provided support to accelerate study start-up. The Research Studio program completed 12 consults with excellent feedback on satisfaction. The TIN Hub Liaison Team reviewed and assisted with the submission of 1 application to the Trial Innovation Network. The initial consult was in progress as of February 2024. The team also received 3 expressions of interest, 1 of which had a PI identified. The two CTRC Core labs located at CU Anschutz consolidated their study feasibility reviews into a single review to decrease study start-up time and complexity.

3.2 RKS Enhancements for Clinical Trial Management System (CTMS; OnCore) expansion and IND/IDE support. The CHCO *Research One* project to eliminate separate clinical and research Hospital Account Records (HARs) and optimize Epic for research was completed and went live. This included improvements to the decision trees for research scheduling at CHCO and other enhancements to reduce the administrative burden of research visits for investigators and study teams. OnCore was updated to include all CHCO research studies and enrollment data for each study was entered in preparation for full Oncore and Epic integration.

The IND/IDE Office in the Office of Clinical Research Operations and Services was launched in July 2023 and provides support for all non-oncology and institutionally sponsored studies; the Colorado Cancer Center provides this support for oncology studies. The program was developed to support central oversight and support of all INDs and IDEs held on campus. The IND/IDE office is staffed with 7 members, including a Project Manager, Pharmacovigilance Specialist, three Regulatory Specialists, and a Regulatory Support and Platform Specialist, plus two medical directors. The office supported 17 single patient compassionate use applications, 28 full IND/IDE applications, and 35 consultations with study teams in this reporting period.

3.3 CTRC contributions to acceleration of clinical trials. Dedicated research services were added to CTRC offerings to increase the efficiency of research, including Fibroscan liver elastography measurements, which were difficult to schedule using hospital resources, and advanced musculoskeletal imaging via HR-pQCT.

The CCTSI Research Operations and Strategic Integration (ROSI) service, part of the Continuous Process Improvement team, worked to identify two major projects to improve the CTRC clinical research study experience and reduce overall start-up time and complexity: 1) a CTRC start-up dashboard encompassing all Cores and CU Anschutz locations (adult and pediatric inpatient and outpatient), and 2) a comprehensive CTRC user guide for clinical research coordinator orientation and instructions, consolidated across all Cores. The comprehensive CTRC User Guide incorporates user SOPs for all Cores. The CTRC start-up dashboard leverages the system built under the last UL1 award that won a 2023 CU system-wide Innovation and Efficiency Award. The start-up dashboard now covers adult nursing, CHCO nursing, Anschutz Core Labs, Nutrition, cardiovascular imaging, and APP services. It tracks Core feasibility reviews, investigator responses to concerns or requests for further information, approval dates, and version tracking for draft nursing orders and lab instruction guides. This system is designed to dramatically reduce the number of emails for CTRC staff and study teams and streamline study operations. It also enhances cross-Core communication and ability to launch new protocols more quickly. This system is currently undergoing beta testing.

Goal 4: Ensure that R&S operations can respond to urgent public health emergencies

CCTSI leaders and CTRC managers were actively involved in the CHCO Research One project and launch that decreased research complexity. The CCTSI ROSI service expanded process improvement services from the pediatric CTRC to the adult CTRC for Core integration and to improve readiness for future public health emergencies. Because companion and wild animals are susceptible and may act as reservoir species or as agents of variant spillback during public health emergencies, the new Veterinary Clinical Trials Coordinator (Dr. Tracy Webb) is poised to respond to such emergencies through her interactions with industry and academic partners to guide communication, identify DVM-MD partnerships, support multi-institutional regional and

national clinical trials, provide regulatory, budget, and logistical support, and implement veterinary 'smart IACUC' tools.

Goal 5: Enhance recruitment and retention of diverse research participants

The Study Monitoring Committee (SMC), chaired by Catherine Jankowski, PhD, continues to track enrollment in clinical trials and provide targeted resources to PIs of under-performing trials. In the reporting period, the Study Monitoring Committee provided resources for 20 protocols.

5.1 Inclusion of older adults. An innovative pathway to encore careers in research was created for older adults who are un/underemployed. The program trains older adults for specialized community-facing and participant-centered roles on clinical trial teams to increase the recruitment and retention of older adults and other underrepresented populations in clinical trials. Older Adult Research Specialists (OARS) roles include: 1) developing effective communication and outreach strategies to engage older adults from diverse backgrounds in research; 2) recruiting and consenting participants for trials; 3) supporting retention by identifying barriers to study participation and connecting study participants with needed resources to address social needs; 4) educating research teams regarding key considerations for including older adults in research, anchored by the Geriatric 5Ms, to inform trial design and implementation; and, 5) catalyzing research innovations to increase representation in research. The program has trained 43 OARS, including 16 in the current grant year. Graduates have been hired as research coordinators at CU Anschutz by research teams from several academic units and at the Rocky Mountain Regional VAMC.

OARS also implement Research Roadshow events with community partners to connect research with local life and community culture. In the current grant year four Research Roadshows reached 634 individuals: BeaconFest in Grand Junction; wellness-focused fair at the Center for African American Health; AgeTech Research Roadshow at Senior Planet; and, the campus-based *Geriatrics and Aging Research Symposium*. Respondents reported increases in the degree to which they agreed with statements such as "*Researchers can be trusted*" and "*Researchers care about me and people like me.*"

5.2 Inclusion of minority and underserved populations. The Clinical Research Recruitment Program was formed in 2022 and, after beta testing in 2023, launched a recruitment consultation service in December 2023. The Consult Service completed 14 consults with different study teams to develop recruitment plans and advise on social media and other forms of recruitment that can target specific demographics. The program is intentionally ramping up slowly to build capacity but has already launched social media recruitment campaigns for 7 studies. This program is the institutional partner for ResearchMatch.

B4: What opportunities for training and professional development has the project provided?

Several R&S programs supported opportunities for training and professional development:

- The Natural Animal Models Core developed guidance for veterinary multi-center trials, best practices for veterinary regulatory compliance and bio-archive management, and promoted advocacy, training, and communication efforts. They led training and implementation of Lab Key Sample Manager software for CSU veterinary researchers to support bio-archive management and sample sharing. The Core has also been developing an online training course for members of veterinary research teams to help them navigate the regulatory landscape; the expected release date is July 2024.
- The Clinical Research Recruitment Program helped to develop Skillsoft training on recruitment and provide resources and training to study teams through the consult service.
- The Decentralized Clinical Trials (DCT) Program assembled a Community of Practice (first meeting, February 2024) to provide ongoing opportunities for information sharing and best practices development. Educational and training program content is in development.
- The DCT Program developed language to support ARPA-H applications and meets with study teams to orient them to this sponsor.
- The CCTSI D&I consult and fee-for-service programs have provided tailored, practical assistance to CCTSI investigators, thereby amplifying the impact of their research-driven innovations.
- The CCTSI D&I consult service co-sponsored a table at the Annual Conference on the Science of D&I (December 2023) to share D&I research core resources and services.
- The Centralized IND/IDE Office conducted35 consultations with study teams.

- The OARS Programs trained 16 OARS during this grant period specifically to connect with older adult communities and facilitate the enrollment of older adults in clinical research.
- The Clinical Research Recruitment Program consultation service has been training study teams to develop recruitment plans and advise on social media and other forms of recruitment to catalyze the enrollment of individuals from diverse and under-represented backgrounds.
- The BERD held several short courses to complement traditional course work: Statistical Literacy I, Statistical Literacy II, Fundamentals of Study Design, Fundamentals of Data Science Literacy, Fundamentals of Data Visualization, Fundamentals of Electronic Health Record Data Research, and a new course on Causal Modeling in Epidemiology. During the current award period 71 students enrolled in the courses. The most recent event was the 2nd annual CU Data week with 130 individuals attending various 1-hour tutorials on coding, analysis best practices, and other data related events.

B: What do you plan to do during the next reporting period to accomplish your goals?

All components of R&S will continue ongoing efforts to accomplish Goals in Year 2. Some programs have objectives that are specifically targeted to Year 2:

Goal 1: Provide supervisory oversight of R&S operations

Supervisory oversight of R&S operations. The BERD plans to enhance tracking of usage by URM investigators in Year 2.

Natural Animal Models Core to develop guidance for veterinary multi-center trials, best practices for veterinary regulatory compliance and bio-archive management, and promote advocacy, training, and communication efforts. In Year 2, we plan initial template development of a REDCap recruitment tool built for use by CSU researchers performing clinical trials and will investigate integration with the COHA veterinary SMART IACUC network. The COHA SMART IACUC supports multicenter veterinary clinical trials through an IACUC +/- Hospital Review Board reliance agreement that permits eligible institutions that join to cede review of veterinary clinical research to other participating institutions' IACUC and/or Hospital Review Boards, a set of SOPs to guide implementation of the reliance relationships, and a centralized online system to support sign-on, reliance determinations, and harmonization of study reviews and approvals. Additionally, the Regulatory Aspects of Veterinary Clinical Trials will go live. This is an online course that covers the federal/governmental regulatory landscape associated with the conduct of veterinary clinical trials and list the regulatory steps necessary for conducting a veterinary clinical trial so that researchers can appropriately apply regulatory requirements and best practices to veterinary clinical trials.

Disseminating Information about current and new R&S. The Communication and Marketing Core will disseminate information using the following tactics: weekly email announcements to CCTSI Members; CCTSI website content; Found in Translation newsletter (quarterly) for Members; The Link CCTSI staff newsletter (bimonthly); CCTSI events and trainings newsletter (monthly); stories and press releases on the CCTSI newsroom of the website; events calendar to promote programs and courses online; infographics; whiteboard videos; social media marketing; and events such as Town Hall meetings and conferences.

Goal 2: Develop expertise and capacity to support Virtual and Real-World clinical trials

Pragmatic Trials Navigation Service. Conduct annual resource catalog audit and update and work collaboratively with the VCT Program to provide resources for EHR-embedded pragmatic trials.

Establishment of a Virtual Clinical Trials Core. We plan to introduce part 11 e-consent vendors for non-EHR embedded studies and actively pursue ways of facilitating in home visits (through traveling nurses and research coordinators).

D&I Research Core services. In year 2, we will deploy the tools developed in Year1 to build a robust fee-for-service consult service.

Goal 3: Accelerate start-up and completion of Clinical and Translational Research studies

RKS Enhancements for CTMS expansion and IND/IDE support. The work subsequent to the CHCO "Research One" project is the full integration of OnCore (CTMS) with Epic which will occur in Year 2 and continued support for all AND/Ide studies at CU Anschutz.

CTRC Contributions to acceleration of clinical trials. In Year 2, the comprehensive CTRC User Guide will be completed through integration of individual Core SOPs and launched. The CTRC start-up dashboard will be beta tested internally, then by user advisory board (UAB) members, before going live.

The CTRC Network also plans to launch a campaign to attract new investigators to conduct their protocols on the CTRCs. The plan is to meet with groups of investigators in a department or division, make them aware of the R&S available to them, and have a PI in the academic unit provide an endorsement for the CTRC.

Goal 4: Ensure that R&S operations can respond to urgent public health emergencies

Following deployment of the CTRC User Guide and start-up dashboard, the CCTSI ROSI program will work with the Evaluation Core to assess outcomes and conduct cycles of iterative improvement and consult with the UAB and CTRC Cores to identify and prioritize new high-impact projects.

Goal 5: Enhance recruitment and retention of diverse research participants

5.1 Inclusion of older/elderly adults. The Older Adult Research Specialist (OARS) program may suspend training during the next grant year and focus on Research Roadshows because the hiring demand for OARS has plateaued.

5.2 inclusion of minority and underserved populations. The Clinical Research Recruitment Program plans to expand support for social media campaigns to aid URM recruitment.

C2: Website(s) or other internet site(s)

- The D&I Core website (https://cctsi.cuanschutz.edu/resources/dissemination) points to products developed by the CORE (e.g., Dissemination How To Guides) that assist investigators with the planning and conduct of D&I research.
- Following beta-testing of a new service model, the Clinical Research Recruitment Program developed a website (https://research.cuanschutz.edu/university-research/special-initiatives/recruitment/social-media-for-research-study-recruitment) to assist investigators with recruitment through the use of social media.

C3: Technologies or techniques

- The CCTSI IT team worked with CTRC Cores to develop the electronic CTRC start-up dashboard that won a 2023 CU system-wide Innovation and Efficiency Award. The start-up dashboard now covers adult nursing, pediatric nursing, Core lab, nutrition, cardiovascular imaging, and APP services.

E2: What is the impact on physical, institutional, or information resources that form infrastructure?

- The Clinical Research Recruitment Program and Clinical Research Workforce Development Program are both institutional resources that are growing and are supported by the UM1 award.
- The Natural Animal Models Core, in collaboration with colleagues at Tufts University, is generating online training courses that will enable investigators to adhere to regulatory requirements and apply best practices to veterinary clinical trials.

UM1 Year-1 Report: Element D, Module 2 - Clinical and Translational Science (CTS) Pilots
Report Period: 9/15/2023 - present

B1: What are the major goals of the project

The Clinical and Translational Science Pilot Grant Program (**CTS-Pilots**) accelerates translational and clinical science by providing a funding platform for new ideas, methods and collaborations among Members and Stakeholders from all CCTSI Partner Institutions.

The CTS-Pilots provide one-year awards to develop new ideas, methods, and collaborations, and to address translational science roadblocks, customarily supporting junior CTS researchers through the **Strategic Goals:**

Goal 1. Accelerate the REDCap-based Pilot Award application process to provide valuable support to CTS researchers and address needs and barriers in planning, conducting, analyzing, and disseminating CTS studies

Goal 2. Provide a rigorous peer-review process for selection of the best CTS pilot applications using a unique REDCap-based database to match the scientific focus of the proposal with reviewer expertise.

Goal 3. Conduct a comprehensive evaluation to monitor productivity and efficiency of CTS-Pilots awards during their funding period, and to follow-up on the success of awardees and the impact of their projects

Goal 4. Disseminate our REDCap peer-review process platform to CTSA Hubs for implementing fast, efficient, and transparent Pilot Grant Management to facilitate CTS-Pilots nationally.

B2: Accomplishments

Goal 1. Accelerate the REDCap-based Pilot Award application process to provide valuable support to CTS researchers and address needs and barriers in planning, conducting, analyzing, and disseminating CTS studies: The major focus of CTS-Pilots is to support the initial stages of innovative projects with the ultimate goal to accelerate their clinical and translational application and to spark creative solutions to complex health problems. CTS-Pilots provides one-year awards to develop new ideas, methods, and collaborations that advance CTS, customarily supporting junior researchers at all CCTSI Partnering Institutions.

Four programs in CTS-Pilots are integrated across Discovery (T0.5-T2) and Community-Population (T3-T4) translation: (i) Colorado **CO-Pilots**; (ii) Child-Maternity Health **CMH-Pilots**; (iii) Community Engagement **CE-Pilots**; and (iv) Translational Method **TM-Pilots**. Since the last report, following the FOA guidelines, we have increased the dollar amount for each award and awarded the FOA-mandated maximum of 8 Pilot Awards in the first year, with the funding period 09/01/2024 – 08/31/2025.

CTS Program	Annual Budget	1st year # award
Colorado Pilots	**$140,000**	**3**
Mentored Pilot	$40,000	
Early Career Diversity Pilot	$40,000	
CU-CSU Collaborative Pilot	$60,000*	
Child and Maternal Health Pilots	**$80,000**	**2**
Mentored Pilot	$40,000	
Junior Pilot	$40,000	
Community Engagement Pilots	**$25,000**	**1**
Joint Pilot	$25,000	
Translational Methods Pilots	**$60,000**	**2**
Innovation Pilot	$30,000	
Bioinformatics/Biostatistics	$30,000	
Total*	**$305,000**	**8**

Colorado CO-Pilots: Three (3) CO-Pilots were awarded to support research across all disciplines, all disease areas, and at all CCTSI Partnering Institutions.

- One Mentored Award ($40,000 a year; an increase from $30,000) for early-stage investigators (post-doc fellows, instructors, asst. professors) with mandatory multi-disciplinary mentorship and cross-disciplinary training.
- One Early Career Diversity Award ($40,000 a year; an increase from $30,000) for URM junior faculty (instructors, assistant professors). Mentorship is not required.
- One CU-CSU Collaborative Award ($60,000 a year) for experienced investigators developing projects that require new cross-institutional (CSU-CU) collaboration. Projects that use natural animal models of human disease as well as other unique CSU resources to overcome existing roadblocks in translational science will be given priority. This award requires co-PIs from both CSU and CU.

Child and Maternal Health (CMH) Pilots: Two (2) CMH) pilots were awarded which address obstacles in performing cross-disciplinary and cross-institutional research in children, pregnant women, and mother/child pairs, which will improve child and maternal health and prevent diseases that begin in early life:

- Mentored Award ($40,000 a year; an increase from $30,000) for early-stage investigators to benefit from strong

mentorship and cross-disciplinary training in clinical and translational research.
- Junior Faculty Award ($40,000 a year; an increase from $30,000) for instructors and assistant professors. Mentorship is not required.

Community Engagement (CE) Pilot: One (1) CE pilot was awarded to support a "Joint Pilot" that is a partnership between academic researchers and community organizations or individuals to address health disparities or inequities. $25,000/yr was awarded (an increase from $20,000) for a well-defined joint research project (community-academic co-PIs required) that addresses a community-based translational science problem while obtaining preliminary data for future grant applications.

Translational Methods (TM) Pilots: Two (2) TM pilots were awarded for innovative technology developments to address roadblocks and advance translational science:

- One Innovation Award ($30,000 a year; an increase from $20,000) to develop novel cutting-edge methods, processes and technologies (devices, assays, digital, science of team science) to advance translational science.
- One Biostatistics/Bioinformatics Award $30,000 a year; an increase from $20,000) to develop innovative statistical approaches, artificial intelligence algorithms, and bioinformatics software to address analysis of complex biomedical data sets.

Program governance. The CTS Pilots are led by the CTS-Pilots Steering Committee, chaired by Dr. Serkova (CTS-Pilots Director, CO and TM-Pilots Director), and includes the 4 Co-Directors: Drs. VandeWoude (CO-Pilots), Nease (CE-Pilots), Zeitler and Baker (CMH-Pilots). The Co-Directors report to Dr. Serkova and oversee the specific type of pilot award including solicitation of applications, review, and prioritization. Dr. Serkova sits on the CCTSI EC and report to Dr. Sokol, CCTSI MPI. The CTS-Pilots team will interact closely with the CTRC Network, BERD, Clinical Trials, Pragmatic Trials, Natural Animal Models, and D&I programs to ensure awardees benefit from these resources.

Fiscal management. A total of **$305,000** in CTSA grant funds were allocated in the Year 1 to CTS-Pilots to support 8 projects. Each awardee has an account set up through the CCTSI Administrative Core. Personnel costs, consumables, Core services, and other expenses are paid from these accounts, which are monitored for compliance with all institutional and federal regulations. Systems for fiscal management have been established through the CCTSI Administrative Core which provides awardees with reports of spending, balances, and cost management on a regular basis.

Solicitation of applications. Solicitation for new applications occurs annually in September and is advertised on the CCTSI website and through email announcements from the Deans' offices, the CCTSI, CTS-Director townhalls, and email to all faculty and trainees at Partner institutions and affiliated community organizations. A Letter of Intent submitted by November is mandatory to allow the Administrative Team to assist individuals prior to submission of a full application in January and to choose appropriate reviewers using our REDCap Pilot Platform. To ensure compliance with federal and NIH policies, each applicant (as relevant) must describe inclusion of human participants, model organisms and animal welfare, genetic testing, and/or stem cell research and address the "translational science roadblock" requirements outlined in NIH policies. Several Informational Calls are offered by the Program Directors to explain the goals and the application process to potential applicants.

Goal 2: Provide a rigorous peer-review process for selection of the best CTS pilot applications using a unique REDCap-based database to match the scientific focus of the proposal with reviewer expertise: CO-, CMH- and TM-Pilot applications are subject to similar review criteria based on the standard NIH review template and scoring system. The REDCap Pilot Platform, with its comprehensive expert reviewer database, ensures the optimal expertise match between the scientific focus of the proposal and two selected reviewers. Applications are initially reviewed and scored by a primary and secondary reviewer, and scores averaged. A Study Section Panel is held for each of the 4 Pilot Programs, operating in the NIH fashion, so the most meritorious applications receive discussion whereas applications deemed less meritorious will not be discussed. Each application is scored and ranked by average impact score. Factors considered in the scoring include: innovation; scientific merit; translational science significance and roadblocks; relevance to the CCTSI mission; investigator and team credentials; environment and use of CCTSI resources; and community participation, if relevant. CE-Pilot applications have a unique focus and will be reviewed under a separate

rubric: The PACT Pilot Grants Committee reviews all CE-Pilot applications and identify those that have the greatest potential to improve community translation and potential to decrease health disparities. All applicants receive full written reviews from two reviewers.

Prioritization of Applications: The CCTSI EC receives a formal report with recommendations for funding based on final impact scores. Applications with widely discrepant scores, virtual "ties," and applications that border the funding range are discussed at length. The CCTSI EC provides final approval of funding. The CTS-Pilots Program **does not** fund "translational research projects" (which are focused only on crossing a particular step of the translational process for a particular target or disease) that do not also address a generalizable translational roadblock, in accordance with NCATS guidelines (PAR 21-293). Awarded projects have to meet all institutional and NCATS Prior Approval requirements before award funds are released.

Goal 3. Conduct a comprehensive evaluation to monitor productivity and efficiency of CTS-Pilots awards during their funding period, and to follow-up on the success of awardees and the impact of their projects: 1) Timely completion of regulatory requirements by PIs; **2)** Interim (6-month) and close-out (12-month) progress reports; and **3)** annual follow-up for 5 years using Evaluation Core surveys, including assessment of ROI. Progress reports describe study enrollment, limitations, analysis of data, and dissemination of results. **Metrics** include dissemination and generalizability of solutions to translational science obstacles, publications, external funding, patents and novel innovations, initiation of novel clinical trials, and collaboration among awarded investigators. Novel methods developed by CTS TM-Pilots are shared with I-Corps and CU Innovations for potential commercialization and dissemination across the CTSA consortium. Dissemination of the REDCap peer review infrastructure to the CTSA consortium is tracked by the number of CTSA hubs who participate in virtual training and workshops, conducting surveys and interviews with participants, and sharing results with the CTSA consortium.

Triennial Needs Assessment Surveys of CCTSI members and non-members of CCTSI assess benefits and obstacles encountered by CTS-Pilot applicants, and this feedback is used to modify the program. Our Evaluation Core/CQI program uses these metrics to make recommendations to the EC for continuous QI.

Goal 4. Disseminate our REDCap peer-review process platform to CTSA Hubs for implementing fast, efficient, and transparent Pilot Grant Management to facilitate CTS-Pilots nationally: Mrs. House discussed the Colorado CTSA Hub REDCap based application and review platform on the QA/QC working group call and offered to assist with consultation on implementation for sites who may be interested. She was contacted by 6 other hubs with questions and interest in adopting to the platform for their sites.

B4: What opportunities for training and professional development has the project provided?

The CTS Pilots are tightly integrated with the objectives of career development in that Mentored and Junior Faculty Pilot Grant awards are designed to directly assist early career investigators and to help more experienced investigators form inter-institutional and academic-community collaborations.

B5: How have the results been disseminated to communities of interest?

We disseminate our innovative REDCap infrastructure through peer-reviewed publications and presentations at the CTSA Program Annual Meetings, in collaboration with the CCTSI D&I Core. The REDCap Pilot Grant Management System is offered through virtual training and workshops to interested CTSA Hubs for implementing fast, efficient, and transparent CTS-Pilots Infrastructure to facilitate and accelerate translational research locally, regionally and nationally. Dissemination of the REDCap peer review infrastructure to the CTSA consortium are tracked by the number of CTSA hubs who participate in virtual training and workshops, conducting surveys and interviews with participants, and sharing results with the CTSA consortium

Novel methods developed by CTS TM-Pilots are shared with I-Corps and CU Innovations for potential commercialization and dissemination across the CTSA consortium.

C2: Website(s) or other internet site(s)

Nothing to report

C3: Technologies or techniques

Nothing to report

E2: What is the impact on physical, institutional, or information resources that form infrastructure?

Nothing to report

Element D3: Health Informatics

B1: What are the major goals of the project

Goal 1: Integrate clinical, biological, administrative, and public health data and deploy robust analytical environments

Goal 2: Improve accessibility and interoperability of regional and national data sharing and analytics

Goal 3: Develop, validate, and deploy clinical decision support and clinical trial execution tools

Goal 4: Expand hands-on translational informatics education for various career stages and disciplines

B2: Accomplishments

Goal 1: Integrate clinical, biological, administrative, and public health data and deploy robust analytical environments

- Under the leadership of Chief Research Informatics Officer Melissa Haendel, PhD, the CCTSI continued to be heavily involved with the National COVID Cohort Collaborative (N3C).
  - Dr. Haendel and her team continued to provide the backbone of the administrative leadership for N3C during the reporting period.
  - Children's Hospital Colorado and UCHealth data continued to be submitted to N3C. Our campus has an approved data use agreement (DUA) for campus investigators to use N3C.
  - Dr. Haendel was contact PI) on an $11.5M grant funded in late 2021 for N3C to be one of the three EHR cohorts involved in the NIH Post-Acute Sequelae of COVID (PASC) RECOVER Initiative. This grant supports rapid-cycle analytics on the N3C platform (SA 2) as well as data augmentation (SA 1).
  - Dr. Haendel led the "tenant model" pilot project that leveraged N3C infrastructure. It focused on 3 disease models (Alzheimer's Disease, Renal Disease, and Chronic Pulmonary Lung Disease) to provide research with a secure computing platform to conduct analyses to address local and national questions to advance scalable research. Both UCHealth and CHCO participated as one of ten Data Contributing sites. They were members of the Governance Committee, which made decisions concerning the membership and voting structure for the tenant pilot. UCHealth contributed data and participated in all three pilot projects.
  - Dr. Bennett's R01 Supplement to maintain and extend the pediatric COVID-19 dashboard based on N3C data and monitor for emerging clinical phenotypes of COVID-19 in children led to the identification of a relationships between high rates of viral respiratory infections in adults and children and subsequent development of invasive bacterial infections. A manuscript is under review.
- The $8+M CTSA Supplement funded in early 2021 to study the real-world effectiveness of anti-SARS-CoV-2 monoclonal antibodies in outpatients (PIs Adit Ginde, Ronald Sokol) continued to be productive. Dr. Bennett and his team built the informatics pipeline for the project, which integrates and curates data from Health Data Compass/UCHealth, the local safety net health system (Denver Health), state vaccination systems, the state all-payer claims database, and prospectively collected survey data collected using REDCap. The project involves collaboration with several other components of the CCTSI including the Biostatistics, Dissemination and Implementation, and CReST teams. Manuscripts during the UM1 period include PMID 38384380 and two others in press.
- 2023 REDCap usage metrics: 11,311 active projects (2022: 9,689) and 6,641 active users (2022: 6,156).

Goal 2: Improve accessibility and interoperability of regional and national data sharing and analytics

- Health Data Compass (HDC) continues to use the Observational Health Data Sciences and Informatics (OHDSI) OMOP Common Data Model, which uses a wide range of standard terminologies including SNOMED, RxNORM, and LOINC (plus others). HDC maps idiosyncratic local codes into OMOP standard codes which enables data sharing within the OHDSI community and also accelerates creating data sets with standardized codes.
- The EUREKA analytics environment continues to be a critical campus resource. The current version includes web-based login and internet access with whitelisting of specific resources such as code repositories (e.g. Comprehensive R Archive Network (CRAN) and Anaconda). EUREKA is an infrastructure service in which virtual machines (VMs) on Google Cloud Platform (GCP) are rapidly provisioned for users. The VMs are pre-configured to meet the HIPAA security and compliance standards of Health Data

Compass and its partners (UCHealth, CHCO, the University of Colorado Denver, and CU Medicine). Each EUREKA instance comes with a unique GCP project that includes Google Big Query, Google Storage, a Linux VM, and a Google Cloud Source repository. A wide variety of data science tools are included. Computational and storage resources and widely scalable, but users pay only for their actual EUREKA costs.

Goal 3: Develop, validate, and deploy clinical decision support and clinical trial execution tools

- Dr. Bennett, in his role as contact PI for an R01 to develop and validate a novel data-driven pediatric sepsis definition and criteria and as Analytics Co-Lead for the International Pediatric Sepsis Definition Task Force, completed work on the new Phoenix pediatric sepsis criteria and disseminated them in two simultaneous manuscripts in *JAMA* in January 2024 (PMIDs 38245897, 38245889). That project leveraged EUREKA and highlight its benefit to the campus: data from 6 U.S. sites and 4 international sites are being computed on using EUREKA with secure co-development by investigators from several centers. CDS deployment of the criteria on Epic's Cognitive Computing Platform (ECCP) is one next step in that work.
    - Dr. Bennett and a mentee, Dr. Blake Martin, have partnered with CHCO IT personnel to deploy on ECCP a dynamic tool predicting serious bacterial infection at the time of ICU admission. The tool is currently running silently and Dr. Martin is collecting prospective validation data.
    - Dr. Bennett continued as a member of the UCHealth Clinical Intelligence Steering Committee.

Goal 4: Expand hands-on translational informatics education for various career stages and disciplines

- The video tutorials developed by the CCTSI REDCap team continue to see wide use (73,838 views on youtube and ~16,800 views on vimeo during 2023).

B4: What opportunities for training and professional development has the project provided?

- Bennett: Committee member for two PhD candidates.
- Bennett: Mentored 5 research faculty, 6 clinical faculty, and 3 graduate students focused on informatics and data science.

B5: How have the results been disseminated to communities of interest?

Nothing to Report

B: What do you plan to do during the next reporting period to accomplish your goals?

Continue the methods described above to achieve the four specific aims

C2: Website(s) or other internet site(s)

Nothing to Repor.

C3: Technologies or techniques

Nothing to Report

E2: What is the impact on physical, institutional, or information resources that form infrastructure?

Nothing to Report

UM1 Element E: Pragmatic EHR Embedded Trials Research Program

B1: What are the major goals of the project

Goal 1: To build the PEET Research Program infrastructure and governance needed for prioritization and support of proposed Pragmatic EHR-embedded Clinical Trials throughout the UCHealth system.

Goal 2: To engage stakeholders in co-design of user guidance materials and protocols for implementation of PEET infrastructure and "designing for dissemination" across the CTSA consortium.

Goal 3: To conduct a pragmatic EHR-embedded clinical trial and use lessons learned to inform user guidance for a broad range of subsequent EHR-embedded clinical trials (up to 2 ongoing per year) to be funded through this mechanism over the 7 years of the UM1 award.

B2: Accomplishments

Goals 1 & 2: The Pragmatic EHR-Embedded Trials (PEET) Research Program element is led by Co-Leaders Adit Ginde, MD, MPH and Bethany Kwan, PhD, MSPH., and has focused its first year on building its team, advancing key infrastructure partnerships, and selecting a second demonstration project to gather additional learnings about the current state of campus and health system infrastructure as it impacts EHR-embedded pragmatic trials.

- In Year 1, work on PEET's first demonstration project ("A Randomized, Pragmatic, Adaptive trial of Metformin for Glucose Intolerance or Increased Body Mass Index in Prostate Cancer Patients") was undertaken in collaboration with project PI Thomas Flaig, MD. The goal of this project is to test the feasibility of enrolling patients who have glucose intolerance and/or increased BMI to a randomized pragmatic study of metformin plus lifestyle modification information versus lifestyle modification information only. As of January 2024, over 1,000 participants had consented to initial data collection, and 21 have consented and enrolled in the RCT (6 to metformin, 15 to lifestyle-only).
- In January 2024, PEET invited concepts for a second demonstration project, to support momentum at UCHealth by leveraging CCTSI grant funds, gain learnings from demonstration project representing current, post-pandemic capabilities, and continue moving the program forward while allowing time to fully develop a formal RFA process (planned in Year 2). Seven project concepts were received, and three formal proposals were invited. Final project review and prioritization by the Steering Committee is underway and projected to be completed in April 2024. The selected proposal will be shared with NCATS for final approval by June 2024.
- A crucial element of the PEET program is collaboration with UCHealth to develop the infrastructure and governance needed for prioritization and support of proposed pragmatic EHR-embedded clinical trials throughout the UCHealth system. Since 9/15/2023, the PEET team has held several meetings with a cross-functional UCHealth team including leadership, informatics, regulatory and research administration, to outline the scope and determine staffing needs to build out Epic infrastructure and governance, and assure strategic alignment of a second demonstration project.
- PEET's Steering Committee provides oversight and subject matter expertise across multiple scientific and technical domains, and also includes key decision-makers from CU and UCHealth. The Steering Committee held its first meetings in February and March 2024, and will continue to meet quarterly to review progress towards EHR infrastructure & emerging PEET implementation guidance; review progress of demonstration studies; advise on operational improvements; and act as consultants for the UCHealth and project research teams during implementation.
- In December 2023 the PEET team added a program manager (0.2FTE), and in January 2024 began a search for a full-time Senior or Principal Research Services Professional to support the program.

Goal 3: A progress report for the first PEET Demonstration Project (*A Randomized, Pragmatic, Adaptive trial of Metformin for Glucose Intolerance or Increased Body Mass Index in Prostate Cancer Patients)* follows this report.

B4: What opportunities for training and professional development has the project provided?

Nothing to Report

B5: How have the results been disseminated to communities of interest?

Nothing to Report

B: What do you plan to do during the next reporting period to accomplish your goals?

In the next grant year, PEET will launch its second demonstration project, projected to be finalized in April 2024 and implemented starting summer 2024. In concert with this project, PEET will continue to work closely with both the Steering Committee and the UCHealth infrastructure group to support the development of clinical informatics infrastructure and governance. In addition, the PEET leadership team will engage with the first and second demonstration project teams to support implementation and also to map processes, barriers, and facilitators to help inform future PEET project selection, design, and implementation.

Another priority in the next year will be engagement with researchers, health providers, patients and health system leadership to co-design user guidance materials and protocols for implementation of PEET infrastructure and “designing for dissemination” across the CTSA consortium. The PEET team will leverage multiple engagement methods, including Community Engagement Studios focusing on promoting trust and equitable participation in PEET trials and addressing concerns about electronic consent processes; and customer discovery, value proposition design and usability testing to promote interest in the PEET RFA among investigators. In consultation with stakeholders and the Steering Committee, the PEET RFA will be launched in the coming year.

C2: Website(s) or other internet site(s)

Nothing to Report

C3: Technologies or techniques

Nothing to Report

E2: What is the impact on physical, institutional, or information resources that form infrastructure?

- Developed demonstration project solicitation and review processes
- Established relationships with UCHealth leadership and Epic analyst teams to facilitate rapid decision making and implementation of PEET projects
- Developed informatics infrastructure in collaboration with UCHealth to support Demonstration Project #1, which will serve as the basis for Demonstration Project #2 and future PEET projects

Evaluation Core Report

Conceptual Framework and Objectives. CCTSI's strategic goals guide The Evaluation Center's (TEC at CU-Denver) external evaluation of CCTSI programs. TEC helps inform and assess progress toward achieving these goals, as well as the specific goals of Elements B-E, through responsive tracking, assessment, and evaluation. The evaluation objectives include: 1) Establish specific metrics to demonstrate local CTSA impact through rigorous program evaluation; 2) Disseminate research results and best practices broadly; 3) Integrate Quality Process and Improvement Plans (QPIP) activities to continuously improve programs and impact; and 4) Participate in national-level efforts to develop metrics and measure the impact of the CTSA program. The evaluation design is grounded in the Translational Sciences Benefits Model (TSBM). The TSBM model includes 30 metrics that demonstrate impact in four domains relevant to Clinical and Translational Research (CTR): clinical and medical benefits, community and public health benefits, economic benefits, and policy and legislative benefits.

Summary. TEC provides evaluation findings to CCTSI leadership and programs throughout the year in the form of timely, actionable briefs and reports. Table 1 provides a summary of planned metrics, data collection methods, and evaluation findings across major grant elements to demonstrate the impact of the CCTSI and identify areas that would benefit from QPIP activities.

Participation in the National CTSA Evaluators Group. CCTSI evaluators will continue to participate in collaborative learning and planning sessions with evaluators from across CTSA hubs including the CCOS Evaluators Group bimonthly meeting, quarterly TSBM discussion group meeting, and monthly CTSA program webinar.

Table 1.1. ELEMENT B. STRATEGIC MANAGEMENT

Metrics	Data Collection Methods	Timeline
a. Utilization of CCTSI resources/services **b.** Satisfaction with resources **c.** Anticipated programmatic needs	**a – c.** Needs Assessment Survey to CCTSI community	• Triennial
Dissemination & Implementation (D&I) Core **a.** TSBM case study library **b.** D&I consulting services	**a.** Development of TSBM case studies, create & post to website **b.** Participant surveys	• Annually

Table 1.2. C1 WORKFORCE DEVELOPMENT (WD)

Metrics	Data Collection Methods	Timeline
Workforce Diversity **a.** % Underrepresented in Biomedical Research (UBR) participation in WD programs	**a.** Application data	• Rolling applications, program specific
Pre-F, Pre-K, Pre-R Grant Review/Mock Study Sections **a.** # of grant applications reviewed, awarded, resubmitted, grant amount **b.** Grants tracked by NIH grant mechanism (NIH RePORTER), Foundation, non-NIH government via longitudinal tracking **c.** NIH success rates compared to national and institutional benchmarks	**a – b.** Post-participation surveys **a – c.** NIH RePORTER	• 3x per year • Annual program summaries across all application cycles
Communicating Your Science to the Public **a.** 20 items measuring effectiveness in communicating scientific messages to the public (E.g., identify key messages, identify patient stories, speak in sound-bites, oral communication, build a digital brand, create short digital stories)	**a.** Post-workshop series evaluation survey	• 3x per year • Annual aggregate program evaluation summary

Teaming for CTR **a.** Team Planning (e.g., Shared language, Shared vision, Ground rules, Creating team charters) **b.** Managing a Team (e.g., Creating meeting agendas, Establishing authorship agreements) **c.** Interpersonal Relations	**a—c**. Pre/post-evaluation survey	• Annually

Table 1.3. C2 COMMUNITY ENGAGEMENT AND HEALTH EQUITY (CEHE)

Metrics	Data Collection Methods	Timeline
a. Number of investigators and professional research staff trained in DEIA and community engagement **b.** Number of Community Based Organizations' (CBOs) trained and readiness to engage in research **c.** Increased network of CBOs willing to partner on research, successful academic and CBO partnerships	**a.** Database tracking **a—b.** Pre/post surveys to assess learnings from training curriculum **b.** Interviews with CBOs to assess knowledge & application of learnings **c.** Development of TSBM case studies	• Annually

Table 1.4. ELEMENT D RESOURCES & SERVICES

Metrics	Data Collection Methods	Timeline
D1. Clinical & Translational Research Centers (CTRCs) **a.** Satisfaction with CTRC sites, resources, and staffing **b.** Utilization of CTRCs and Core services **c.** Collected feedback on billing, implementation of new protocols, and communication with CTRC staff	**a – c.** User Satisfaction Survey **b.** Research visit data from CTRC Scheduler	• Annually
D2. CTS-Pilots **a.** Follow-on funding, Return on investment (ROI) **b.** Publications and patents **c.** TSBM metrics	**a – c.** Follow up survey with past grantees (for 5 years) **a – b.** Search of secondary databases (e.g. NIH RePORTER /granttome.com) **c.** Development of TSBM Impact Profiles	• Annually
D3. Health Informatics **a.** REDCap users and projects, utilization of REDCap training materials **b.** Publications and grants submitted/awarded as well as projects using new data types **c.** # of students participating in informatics training and certificate programs **d.** TSBM metrics	**a – c.** Database tracking **b – c.** Surveys with training participants **d.** Development of TSBM Impact Profiles	• Annually

Table 1.5. ELEMENT E PRAGMATIC EHR EMBEDDED TRIALS (PEET) PROGRAM

Metrics	Data Collection Methods	Timeline
a. # of demonstration projects reviewed, awarded **b.** Awarded projects' publications and follow-on funding **c.** EHR implementation metrics (program specific, TBD)	**a—b.** Database tracking **c.** Development of TSBM Case Studies & Impact Profiles	• 2027-28

K12 RPPR Narrative

B1: What are the major goals of the project?

The goal of our CCTSI K12 Program is to provide protected time and opportunities for an intensive, mentored career development experience that leads to independent extramural support and leadership positions in CTR and academia.

Objective 1: Individualized Career Development Plan (IDCP) to support core Clinical Translational Science (CTS) knowledge and growth.

Objective 2: Evidence-informed mentoring training by scholar-mentor dyads.

Objective 3: Professional/managerial training, including DEI principles.

Objective 4: Academic writing disciplines; dissemination/communication strategies.

Objective 5: Relationship building with key stakeholders/members across scientific ecosystem.

Objective 6: Connection to innovative CTS programs.

Objective 7: Equitable recruitment processes and enhanced training of underrepresented groups.

B2: Accomplishments

Our K12 program commenced funding 12/01/2023. Three existing KL2 scholars rolled into the new program at that time, and five new scholars were appointed in December 2023. Please see attached biographies of scholars who recently completed our program (since last RPPR, April 2022) and the newly appointed K12 scholars.

We have oriented our Scholar group to requirements of the K12 program so proper planning and scheduling can be assured. We recently (March 2024) hired a new K12 Associate Program Director (Kristin Nowak, PhD) to replace Jose Mancilla-Castillo who left the institution. Along with Drs. Burnham and Shomaker, Dr. Nowak will provide programmatic oversight and individual coaching/guidance for the Scholars on the award.

Accomplishments aligned with objectives above include:

1. Scholars have created individualized tracking documents that include required (e.g. RCR training) and optional (e.g. courses) elements of the K12 program to ensure that goals and objectives for the appointment year (12 months) are being scheduled well in advance. In parallel, we are in the process of finalizing a web version of this document that will link goals of scholars to statements of support from their mentors. This document can be accessed by K12 leadership for purposes of coaching, creating summary reports, etc.

2. Existing scholars (and their mentors) have been active participants in the CO-Mentor Program. Newly appointed scholars are planning to undertake the year-long seminar series beginning in the fall, 2024.

3. Existing scholars accessed the Research Management and Leadership Training (RMLT) on-line module series. A subset engaged in certain Team Training modules relevant to their research needs.

4. Scholars have attended the monthly (in-person) K12 seminar series, which has provided opportunities to present their research to peers and K12 leadership. Existing Scholars have utilized the PreK and KTR programs for grant peer review prior to grant submissions. Existing Scholars have served as PreK reviewers (in conjunction with K12 leaders Shomaker and Maclean). Scholars attended the Communicating Your Research to the Public sessions during 2023.

Major planned activities during 2024, aligned with objectives above:

Objective 1. Newly appointed scholars (after 2024) will utilize the newly developed ICDP (Individualized Career Development Plans) for tracking of activities and mentor engagement.

Objective 2. Scholars will be paired to K12 leaders (Burnham, Shomaker, Nowak) for triannual 1:1 coaching and advising. K12 leadership will work with CO-Mentor Directors (Libby, Austin) to develop CO-Mentor Booster sessions for seasoned mentors to learn best practices and provide networking opportunities.

Objective 3. First year Scholars may engage in RMLT training sessions as their schedules permit; during their second award year, scholars are expected to participate in the Teaming Training sessions (hosted with CCTSI/CSU leader, Cross).

Objective 4. Scholars will continue to attend the monthly K12 seminar series, and each is scheduled to present their research ~3 times yearly for feedback. Scholars will attend a national conference related to their research area where they will present research in poster or invited speaker formats and are encouraged to submit their work for presentation at the NCATS K12/T32 virtual speaker series.

Objective 5. Interactive Seminar planned with Del Pino-Jones (Director of DEI Activities for Educational Pillar) with T32 Scholars related to issues in diverse participant recruitment, management of diverse teams, and unconscious bias identification. Interactive Seminar planned with Nease and colleagues related to opportunities to engage Colorado communities in research.

Objective 6. Seminars planned (with T32 scholars) related to intellectual property development (Holers, CU Innovations), and opportunities/how-to engage Bioinformatics support (Bennett).

Objective 7. In fall 2024, release RFA for new Scholar cohorts, including language to augment URM applications, followed by holistic review process. External advisory committee review of program, and individual scholars, with course correction as necessary.

KL2/K12 Scholar Details (NIH Funded Scholars)

This document contains information about scholars in our KL2/K12 program between April 2022 and March 2023, including scholar/mentor information and scientific aims. In summary, of the 14 individual faculty engaged in the program:
86% (12/14) are women.
29% (4/14) were from a background underrepresented in medicine in science.
29% (4/14) are conducting science involving underrepresented populations.
Where noted (*), certain scholars with an appointment at Children's Hospital Colorado (CHCO) are identified.

Meghan Althoff, MD, PhD 12/01/2023 – Current
F / not URM
Instructor
Medicine/Pulmonary Sciences and Critical Care Medicine
Mentors: Fernando Holguin, MD & Sunita Sharma, MD
Metabolic pathways predicting treatment response to asthma medications

SPECIFIC AIMS
Asthma effects more than 8% of adults in the United States, however there are marked racial disparities in asthma morbidity, particularly among the Black population. Compared to White patients with asthma, Black patients experience worse asthma control, have more exacerbations, ER visits, hospitalizations, and asthma-related death. The etiology of these disparities is complex, however differential treatment response to conventional asthma therapies likely plays a role, particularly as Black participants represent a minority of participants enrolled in these clinical trials. The NHLBI's AsthmaNet funded Best African American Response to Asthma Drugs (BARD) is a unique cohort designed to understand treatment response in this population with rich phenotypic and outcome data. While the BARD study found differences in add-on therapy, the *mechanisms driving differences in treatment response remain unknown*, particularly as plasma and sputum eosinophils did not explain differences in treatment response.

The L-arginine and nitric oxide synthesis pathway is important in asthma pathogenesis and morbidity. In a large prospective cohort, *we found novel racial differences in L-arginine metabolites* including increased Larginine/ADMA among Black participants compared to White and variability in arginine availability, including Larginine/ADMA, was strongly associated with increased risks of exacerbations. The impact of L-arginine metabolites on asthma morbidity did not attenuate the racial disparities in asthma outcomes, indicating that there are likely associated metabolic pathways influencing these relationships. They majority of asthma

metabolomic research, including ours, was done in plasma samples, however validation in respiratory samples is important in understanding mechanisms of asthma morbidity. The metabolome captures both genetic and environmental variability, therefore it is important to characterize genetically driven metabolites as this will aid in determining mechanisms of genetic risk in asthma.

The goal of this proposal is to identify L-arginine metabolites and associated metabolic pathways that predict treatment response and to determine the genetic contribution of these metabolic profiles. ***We hypothesize that there are distinct profiles of metabolites associated with nitric oxide synthesis, which correlates with superior treatment response to inhaled corticosteroids.*** Secondary outcomes of asthma morbidity including exacerbations, asthma control, and spirometry will also be evaluated. A better understanding of these pathways will inform novel biomarkers of treatment response and will offer insights into metabolic mechanisms driving poor treatment response and exacerbation risk.

Specific Aim 1: Compare relative concentrations of L-arginine metabolites across tissue types and determine associations between metabolites and treatment responsiveness. *Hypothesis: There will be distinct patterns of L-arginine metabolites associated with treatment responsiveness and this will differ by asthma phenotype.* We will (1a) compare concentrations of L-arginine metabolites in plasma and sputum and (1b) determine associations patterns of L-arginine metabolites and treatment responsiveness. These analyses will be stratified by T2 status and sex to examine metabolite differences by asthma phenotype.

Specific Aim 2: Identify metabolic profiles associated with L-arginine metabolism and treatment responsiveness. *Hypothesis: There will be distinct metabolite profiles associated with T2 inflammation and nitric oxide synthesis among treatment responsive participants.* We will perform untargeted metabolomic analysis on sputum and plasma samples and (2a) assess for interactions with L-arginine metabolites and (2b) determine associations between these metabolites and treatment responsiveness overall and by T2 status.

Specific Aim 3: Determine the metabolic consequences of asthma loci on treatment responsiveness by performing metabolite quantitative trait loci (mtQTLs). *Hypothesis: There will be mtQTLs associated with treatment-responsiveness indicating the presence of genetically driven metabolites.* We will estimate metabolome-wide heritability in the BARD cohort and include candidate metabolites, including L-arginine metabolites, associated with treatment responsiveness that are heritable. We will then perform genome wide association studies of each heritable metabolites to determine associations between SNPs and metabolites and identify mtQTLs. *The expected outcome* of this K12 is an understanding of metabolic changes associated with treatment responsiveness among Black patients. This training in metabolomics and integrative omics will provide the necessary tools to translate these findings into a career focused on mechanisms and clinical tests of treatment
responsiveness in asthma.

Aubrey Armento, MD 12/01/2023 – Current
F / not URM
Assistant Professor
Pediatrics/Sports Medicine
Mentors: Wendy Kohrt, PhD & Christine Swanson, MD
Understanding Exercise Behaviors and the Impact of Pre-treatment Weight-bearing Exercise on Bone Health in Female

Specific Aims: Restrictive eating disorders (EDs), characterized by purposeful restriction of food intake and/or excessive exercise, can lead to reduced bone mineral density (BMD) and increased risk of osteoporosis. The onset of EDs is often during adolescence, which is particularly worrisome as this is the time of peak bone mass accrual, a main determinant of lifetime fracture risk. It is critical to optimize bone health during adolescence to mitigate fragility fracture and osteoporosis risk during adulthood.Weight-bearing exercise promotes bone accrual. Yet, the osteogenic effects of exercise on bone may be diminished by the presence of a restrictive ED, due to low energy availability and/or menstrual dysfunction as demonstrated by the female athlete triad. The presence of compulsive exercise, defined as excessive and obsessive exercise habits, correlates with eating psychopathology, and exercise is often withheld in ED treatment due to compulsive exercise behaviors or weight restoration concerns. The impact of regular weight-bearing exercise on bone health in adolescents with restrictive EDs is unclear, but individualized exercise programs may have benefit for patients with EDs. **The objectives of this study are to evaluate the relationship of pre-treatment weight-bearing exercise on bone health among female adolescents with restrictive EDs and to longitudinally characterize exercise**

behaviors pre-treatment through recovery in this population. The application of high resolution peripheral quantitative computed tomography (HR-pQCT: a non-invasive, low radiation imaging modality) across clinical research settings has recently grown, as it allows researchers to gather information about volumetric BMD, microarchitecture and strength beyond more traditional approaches (e.g., dual x-ray absorptiometry [DXA]). HR-pQCT provides innovative bone quality data that predicts fracture risk independent of DXA-derived areal BMD, and this data is particularly valuable in those with restrictive EDs
given their risk of poor bone health. While more hours/week of weight-bearing exercise in the month prior to treatment has been shown to correlate with higher areal BMD at the hip in adolescents with restrictive EDs,the impact of exercise on bone microarchitecture in this population is not well-described. Additionally, a limited number of studies have described exercise behaviors in adolescents with EDs across the spectrum of treatment, with considerable variability in the reported prevalence of compulsive exercise. Most work has focused on pretreatment exercise behaviors, with minimal data on exercise behaviors during ED treatment and recovery. Enhanced understanding of bone health and the role of weight-bearing exercise prior to and during ED recovery is necessary to inform optimal bone health monitoring and treatment approaches to exercise in this population.

To address these gaps, we will complete the following aims in a sample of female adolescents with restrictive EDs entering the Eating Disorder Program at Children's Hospital Colorado:

Aim 1: Evaluate the impact of pre-treatment weight-bearing exercise on bone density, bone microarchitecture and estimated strength in female adolescents with restrictive EDs.

H.1. At baseline (pre-treatment), female adolescents with EDs who perform habitual weight-bearing exercise will have higher areal BMD at the total body, lumbar spine, and total hip and more optimal bone microarchitecture and estimated strength than female adolescents with EDs who do not perform habitual weight-bearing exercise.

Aim 2: Describe pre-treatment weight-bearing exercise behaviors and exercise behaviors during and after 6 months of ED treatment and recovery, including correlates to compulsive exercise behaviors.

H.2. Those who participate in more hours/week of exercise pre-treatment will demonstrate more compulsive exercise behaviors, but will exhibit reduced exercise duration and reduced compulsive exercise behaviors through treatment/recovery.

Impact and Future Work: This proposal is innovative as it is the first that will assess bone health using HRpQCT and the relationship with pre-treatment weight-bearing exercise in female adolescents with restrictive EDs. Our study will provide useful information regarding both pre-treatment and treatment/recovery exercise behaviors in EDs to inform future studies assessing changes in bone health across time in female adolescents with Eds receiving treatment. The assessment of pre-treatment weight-bearing exercise and its relationship to bone health will provide foundational data for my future K23 award, which will evaluate the impact of exercise on longitudinal changes in BMD, bone microarchitecture and strength throughout ED treatment/recovery. My CCTSI K12 research project will build upon a newly-established partnership with the Children's Hospital Colorado Eating Disorder Program and demonstrate feasibility of conducting a longitudinal study in this population. With the guidance of an expert multidisciplinary mentorship team, completion of the research aims and career development plan as a CCTSI K12 scholar will be a pivotal step in my career path toward becoming a successful independent investigator in the field of the female athlete triad in adolescents.

Katherine Kissler, PhD 12/01/2023 – Current
F / not URM
Assistant Professor
Nursing, Maternal Child Health
Mentors: Teri Hernandez, PhD & K. Joseph Hurt, MD, PhD
Biomarkers for Uterine Fatigue: Toward Precision Diagnosis and Individualized Management of Protracted Labor

Specific Aims

In the United States, the cesarean delivery (CD) rate is well above the rate targeted to balance maternal- fetal risks and benefits, prompting obstetric professional and public health organizations including ACOG, SMFM, and Healthy People 2020 to make reduction of the CD rate a national priority. While CD can be a life-saving procedure, overuse can lead to maternal-fetal morbidity including increased risk for postpartum hemorrhage, infection, surgical injury, and abnormal placentation in subsequent pregnancies. The most common indication

for unplanned CD is failed treatment of protracted labor. Currently, oxytocin augmentation is the only treatment for protracted labor, but our data suggest that augmentation fails to prevent CD in about 30% of women. The pathophysiology of protracted labor that is unresponsive to oxytocin augmentation is poorly understood, limiting innovation to improve outcomes for these patients.

My overarching hypothesis is that uterine muscle fatigue is an unrecognized driver of protracted labor unresponsive to oxytocin augmentation. In women with healthy tissue, oxytocin augmentation stimulates contractions leading to cervical dilation. However, fatigue in uterine muscle tissue may actually be *exacerbated* by continued stimulation, increasing risk for CD and complications caused by uterine atony.The purpose of this proposed research is to identify biomarkers that differentiate healthy, responsive uterine tissue from fatigued, unresponsive tissue. In the future, these biomarkers can be leveraged to innovate targeted strategies to treat uterine fatigue and avoid CD.

Recently, I evaluated known pathophysiologic variations of labor protraction and identified two promising biomarkers of uterine muscle fatigue: amniotic fluid lactate (AFL) and systemic IL-6, a pro-inflammatory cytokine associated with labor. Additionally, I evaluated several measures of uterine activity and identified the power density spectrum of uterine electromyography (EMG PDS) as a third early marker of muscle fatigue. During the K training period, I propose completion of a novel prospective observational study of nulliparous women with protracted labor, defined as cervical dilation slower than the 95th percentile. Using a phenotyping protocol developed in my preliminary work, (under review) I will measure AFL, IL-6, and EMG PDS in real-time, then classify participants into three labor protraction phenotypes based on duration of protraction and birth route: 1. Highly responsive to oxytocin with relatively short protraction (<4 hrs) and vaginal birth; 2. Moderately responsive to oxytocin with extended protraction (>4 hrs) and vaginal birth; and 3. Minimally responsive to oxytocin with extended protraction (>4 hrs) and cesarean birth. I am uniquely situated to conduct this research considering my clinical experience with laboring patients and the rigorous training of my F31 pre-doctoral fellowship including clinical research protocol development, parturition physiology, and linear mixed models. The proposed training plan will advance my expertise through structured training in translational (T2-T3) research, uterine EMG collection and analysis, and statistical predictive modeling. These training goals, along with advanced mentorship in parturition research and career development, will support completion of the proposed research aims and facilitate steps toward implementation of the results in translational/interventional clinical research.

Aim 1: Quantify the differences in EMG and biomarkers between labor phenotypes. Approach: Among 73 nulliparous women with one of three labor phenotypes classified by length of labor protraction and birth route, I will measure and compare markers associated with muscle fatigue and cesareans including AFL, IL-6, and EMG PDS. **H1**: Compared to women who respond to oxytocin augmentation (phenotype 1), those with a poor response (phenotypes 2&3) will have elevated AFL & IL-6 and reduced EMG PDS (i.e. impaired uterine contractility).

Aim 2: Characterize the relationship among markers of fatigue. Approach: In the above sample, I will characterize the strength/direction of the correlations among AFL, IL-6, and EMG-PDS to contextualize the association between biomarkers/EMG and labor phenotype. **H1:** AFL will correlate positively with systemic IL-6. **H2:** EMG PDS will correlate negatively with AFL and systemic IL-6, suggesting low power is associated with higher uterine fatigue and inflammation.

Aim 3: Develop a regression model to predict uterine response to oxytocin. Approach: In the above sample, I will build a hierarchical multinomial logistic regression model predicting labor phenotype using clinical characteristics, AFL, IL-6, and EMG PDS. **H1:** Addition of AFL, IL-6, and EMG PDS will improve prediction of labor phenotype compared to models built using clinical characteristics alone.

Impact: Identifying biomarkers that differentiate uterine muscle fatigue prior to augmentation with oxytocin would lead to a paradigm shift in obstetrics toward precision intrapartum care that targets the underlying pathophysiology, away from the current “one size fits all” approach to treating labor protraction. Following the K training period, I will utilize the expertise gained and leverage the collected data to develop a K-series or early career R-series NIH application to test interventions to recover uterine metabolism.

Christy Niemeyer, PhD 12/01/2023 – Current
F / URM
Assistant Professor
Neurology

SPECIFIC AIMS

Alzheimer's disease (AD) is characterized by amyloid (Aβ) deposition, neuroinflammation, and glial cell dysfunction. Since genetic and environmental risk factors drive AD pathology, risk factor modification is an optimal strategy to prevent AD onset. Recent epidemiological studies have shown that viral infections are strong environmental risk factors for AD, but which pathogens pose the most risk is unknown. The common neurotropic alphaherpesvirus, herpes simplex virus type 1 (HSV-1), is a likely candidate because infection within the central nervous system contributes to AD pathology.

AD is most well recognized as cognitive impairment and memory deterioration. However, AD patients suffer many other symptoms, including anxiety and sleep disorders, appetite, and neuroendocrine disruption. In early AD, before the disease impacts regions of the brain involved in learning and memory, the brainstem the locus coeruleus (LC), is critically affected and vulnerable to AD pathology. Further, the LC is involved in many anxiety, depression, and sleep/wake cycles and may explain underlying non-cognitive deficits seen in AD. Additionally, the LC is vulnerable to outside pathogens, and damage to the noradrenergic neurons in the LC contributes to neuropathology and behavioral deficits in AD. However, our current understanding of whether HSV-1 triggers LC dysfunction in AD represents a major gap in the understanding of AD-associated non-cognitive deficits and avenues for therapeutic intervention.

Our preliminary results found HSV-1 infection in C57Bl/6 mice, and an AD mouse model (5xFAD mice) shows a striking specificity during primary infection for the LC. Our preliminary results show that HSV-1 increases neuroinflammation and amyloid production in the LC in 5xFAD mice. However, there is a critical knowledge gap in our understanding of the mechanisms that link HSV-1 infection to LC pathology in AD and if there are potential therapeutic targets that may mitigate early LC damage.

While HSV-1 infection can be mitigated with antiviral treatment (acyclovir), it does not seem to improve behavioral deficits following infection. Recent research has shown that HSV-1 in wild-type mice can induce behavioral changes, such as increased anxiety. However, acyclovir alone did not mitigate these behavioral changes, suggesting standard antiviral treatment may not be sufficient in improving HSV-1 central nervous system disease.

Recent reports have suggested that a novel drug, vindeburnol, which targets LC damage specifically, may benefit LC health and decrease neurodegeneration of the LC in early AD. Vindeburnol, a plant alkaloid derivative, has been shown in AD mouse models to reduce neuroinflammation, amyloid burden, and non-cognitive deficits such as anxiety. **We hypothesize** that **co-treatment with standard antivirals and vindeburnol will inhibit HSV-1 accelerated AD pathology in the LC and reverse non-cognitive deficits (anxiety, asynchronous sleep/wake cycles) seen in AD.** To test this hypothesis, we will:

Aim 1: Test the novel drug vindeburnol, with and without co-treatment of antiviral acyclovir, to reverse HSV-1 induced amyloid burden and reduce neuroinflammation in the LC in a transgenic mouse model of AD. We hypothesize that co-treatment with vindeburnol and acyclovir will reduce HSV-1-induced microglia activation and AD pathogenesis in 5xFAD mice. Here we will use a physiologically relevant paradigm of HSV-1 infection in 5xFAD and control (C57BL/6) mice to compare AD pathology and markers of microglial dysfunction (microglial morphology, microglial-AB phagocytosis) in uninfected, primary infected, and latency- infected mice that have been treated with vindeburnol, acyclovir or both. We will perform histological analysis in the LC for neuroinflammation and AD (amyloid) and LC (noradrenergic expression) pathology.

Aim 2: Determine if vindeburnol, along with antiviral acyclovir, reduces HSV-1 accelerated non-cognitive functions. We hypothesize that treatment with Vindeburnol will mitigate HSV-1 induced in non-cognitive function, including anxiety, sleep/wake cycles, over acyclovir treatment alone. We will compare changes to HSV-1 infection in control mice (C57BL/6) and 5xFAD mice of both sexes with and treatment of acyclovir alone, vindeburnol alone, and combined treatments, compared to untreated animals. We will use relevant behaviors to test anxiety (light/dark box), sleep/wake cycles (continuous monitoring of locomotion) and learning and memory (novel object). We predict that co-treatment with vindeburnol and acyclovir combine will mitigate HSV-1-induced behavioral changes in 5xFAD mice and controls.

Impact: This project will systematically evaluate the cellular and behavioral mechanism known to be perturbed by herpesvirus infection and whether the novel LC-specific drug vindeburnol, along with standard anti-viral treatment, will mitigate HSV-1-induced AD risk and acceleration. Elucidating these mechanisms is a critical first step in understanding pathogen-induced disease and in developing targeted therapeutic approaches that prevent the onset and slow the progression of AD.

Erin Englund, PhD 11/1/2021 – Current
F / not URM
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Radiology
Mentors: Jane Reusch, MD & Alex Barker, PhD
Evaluation of skeletal muscle microvascular dysfunction in adult- and youth-onset type 2 diabetes with time-resolved, quantitative MRI

Type 2 diabetes mellitus (T2D) affects approximately 9% of the population worldwide, with increasing incidence across the age spectrum. Microvascular complications of T2D (e.g. retinopathy, neuropathy, and nephropathy), contribute to decreased healthspan and increased healthcare cost. Furthermore, work in my mentor's lab has revealed that cardiac and skeletal muscle microvascular dysfunction are associated with reduced cardiovascular exercise capacity (CVEC) and incipient heart failure, two causes of premature mortality in T2D. However, the pathogenic mediators underlying this impaired CVEC in T2D, their relationship to age and sex, and how they respond to interventions such as exercise training, are not clearly understood. This gap in our understanding of the disease can be addressed with tools to quantitatively interrogate vascular function and muscle metabolism.

Existing methods to probe vascular function measure a single aspect of the vascular tree (e.g. macrovascular flow-mediated dilation or measurement of end-organ tissue-level perfusion) and are therefore incapable of evaluating the integrated vascular response to a vasoactive stimulus. Moreover, the measurement of blood flow on its own does not account for changes in underlying tissue metabolism that drive these flow changes. Thus, there is a critical need to simultaneously quantify macro- and microvascular blood flow and oxygenation in order to evaluate flow-metabolism coupling. This capability would help explain the mechanism of impaired exercise tolerance in people with T2D and could serve as a biomarker of disease progression and therapeutic response.

Here, we propose to use a novel, non-contrast magnetic resonance imaging (MRI) method that I recently developed and validated which allows for the high temporal resolution evaluation of the integrated hemodynamic and metabolic response to exercise in skeletal muscle. This method, termed Velocity, Perfusion, Intravascular Venous Oxygenation, and T2* (*v*PIVOT) provides dynamic quantification of bulk arterial/venous blood flow, microvascular perfusion, venous oxygen saturation, and relative muscle oxygenation. *v*PIVOT is the only method capable of non-invasive quantitation of macro- and microvascular blood flow and oxygenation in both the spatial and temporal domain. Due to the simultaneous nature of the acquisition, it is also possible, for the first time, to evaluate the coordination of these events as they apply to flow shunting and oxygen flux. *We have a unique opportunity to leverage ongoing studies (VA-MIX, PI: Reusch; Renal-HEIR, PI: Bjornstadt), tapping into existing recruitment pipelines, physiologic testing visits, and planned interventions to pursue this novel topic.*

While *v*PIVOT is compatible with Siemens MRI scanners, widespread use across campus requires translation to the Philips platform. Furthermore, the *v*PIVOT response *during* an isometric contraction and in people with microvascular dysfunction has not been evaluated. Through the proposed research project, we will address these questions and develop a comprehensive understanding of T2D pathophysiology across a spectrum of age and sex and evaluate adaptive responses to an exercise training intervention. **We hypothesize that the simultaneous, temporally-resolved measurement of macro- and microvascular flow and oxygenation can identify microvascular dysfunction** and specifically (1) that blood flow and metabolism during exercise is impaired in people with T2D compared to BMI-similar and lean controls and (2) that exercise rehabilitation improves hemodynamic and metabolic responses in people with T2D. We propose the following aims:

Aim 1. Translate *v*PIVOT method for use on all MRI scanners across campus and evaluate advanced analysis strategies: Is there a relationship between workload and measured response?
Healthy individuals (n=10) will participate in a multi-parametric MRI exam including *v*PIVOT and phosphorous MR spectroscopy. Data will be collected during an isometric plantar flexion contraction at each of three

intensities (30%, 50%, 70% of maximum voluntary contraction). This study will provide insight into the relationship between oxidative phosphorylation and *v*PIVOT-derived oxidative metabolism in healthy individuals.

Aim 2. Establish normative data of sedentary people with and without T2D across an age and sex spectrum: Can *v*PIVOT detect microvascular dysfunction and impaired oxidative metabolism?

*v*PIVOT will be used to measure temporally-resolved blood flow, oxygenation, and metabolic responses to isometric exercise in sedentary adults and youth with T2D compared to BMI-similar and lean controls (10 adults and 10 youth per sex and per group, n=60 total). The proposed study will define the relationship of microvascular dysfunction and dysmetabolism to CVEC in people with and without T2D across an age and sex spectrum.

Aim 3. Longitudinal study of exercise rehabilitation in T2D: Can *v*PIVOT elucidate the mechanism of improved exercise tolerance?

*v*PIVOT responses (e.g. temporal post-exercise difference of macro- and microvascular blood flow peaks and whole-leg metabolism) will be compared before and after a 15-week exercise intervention (n=20 total). Identification of the effects of exercise training on blood flow and metabolism will provide insights into the mechanism of improvement of exercise rehabilitation in people with and without T2D.

Success of these aims will improve our understanding of the pathophysiology of exercise intolerance in T2D, disseminate tools to enable clin d metabolism, and identify biomarkers
to monitor treatment response.

Silvania da Silva Teixeira, PhD 04/1/2021 – Current
F / URM
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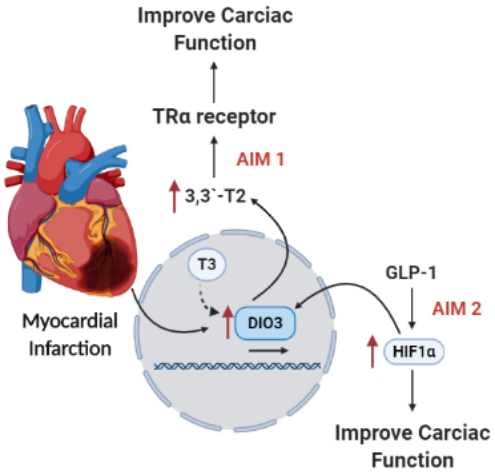
Pediatrics/Nutrition Section, Division of Endocrinology, and Diabetes
Mentors: Darleen Sandoval, PhD & Rebecca Scalzo, PhD
The role of thyroid hormone metabolites on improving recovery from myocardial infarction

Background/Rationale: In the United States, a person will have a myocardial infarction (MI) roughly every 40 seconds. Even with a remarkable decrease in age-adjusted death rates attributable to acute MI, the US's overall number of MI-associated deaths has not dropped since the mid-1970's. MI has a 30% mortality rate, and 5 to 10% of survivors die in the first year of the disease. New treatments for this stunning death rate are needed, and hormonal interventions are understudied. It is known that low serum levels of triiodothyronine (T3) and high levels of reverse T3 (rT3) occur in about one-third of patients following a MI event. Changes in those thyroid hormones (TH) levels correlate with disease severity and poor prognosis and are believed to stem from an increase in the type 3 deiodinase (DIO3) activity, an enzyme that catalyzes the deactivation of T3 into 3,3'- T2. However, in a mice model of cardiac DIO3 inactivation, reduced levels of DIO3 results in restrictive cardiomyopathy. Therefore, whether increased DIO3 activity and the subsequent local T3-deficiency is a protective adaptive response of the stressed heart or a part of a pathologic response leading to the heart's failure remains to be determined.
In this proposal, we will test the premise that the heart's ability to reactivate DIO3 and consequently increase 3,3`-T2 production is essential for MI recovery. Our preliminary data show that 3,3'-T2 acts as a more effective and potent agonist for the thyroid hormone receptor α (TRα), the predominant TR isoform in the heart. Additionally, 3,3'-T2 induces a differential response to regulate genes preferentially modulated by TRα. Although 3,3`-T2 has been considered a biologically inert product of TH catabolism, metabolic effects have been described in rodents. While the potential function in humans remains unknown, high levels of 3,3'-T2 are associated with a decreasing incidence of critical illness. One of 3,3`-T2 metabolic effects involves a significant increase in cytochrome oxidase (COX) activity in hypothyroid animals. COX is the last enzyme of the mitochondrial respiratory chain and plays a fundamental role in aerobic ATP production. It has been shown that the activity of COX is lower after MI, and therapy with a mitochondria-target peptide, which enhances COX activity, improves postinfarction cardiac function. **Therefore, we hypothesize that 3,3'-T2 treatment will improve myocyte mitochondrial function after MI and thus aid with MI recovery (Aim 1) (Fig.1).** Glucagon-like peptide 1 (GLP-1) agonists, which are used to effectively treat type 2 diabetes (T2D) and obesity, have also been shown to improve myocardial recovery after MI. Yet, the mechanism through which this protection occurs is uncertain since GLP-1 receptors are not expressed in cardiac tissues. Since it has been shown that long-acting GLP-1 agonist upregulates DIO3 expression in the pancreas, we predict that GLP-1 improves recovery after MI by increasing DIO3 expression. Also, exendin-4, a GLP-1 agonist, has been

shown to increase the protein levels of hypoxia-inducible factor 1α (HIF-1α), a transcription factor that plays a critical protective function in the pathophysiology of ischemic heart disease. HIF-1α overexpression in the heart promotes angiogenesis, reduces infarct size, and enhances cardiac performance after MI. Interestingly, HIF- 1alpha has been demonstrated to be upstream of DIO3 activation. **Thus, we propose investigating if HIF-1α activation and a subsequent DIO3 upregulation are necessary for the cardioprotection actions aided by GLP-1 after MI (Aim 2) (Fig.1).**



**Aim 1: To test if 3,3`-T2 improves myocardial function after MI.** DIO3 deficient and wild type mice submitted to MI will be treated with IP injections of 3,3`-T2 for 4 weeks. Changes in cardiac morphology and function and cardiomyocyte mitochondrial function after MI will be measured. Changes in DIO3 deficient and wild-type mice will also be evaluated to determine if DIO3 expression is necessary for myocardial recovery after MI.

Aim 2: To determine if HIF-1α and a subsequent DIO3 upregulation are necessary for the cardioprotection actions of GLP-1 after MI. HIF-1α deficient and wild type mice submitted to MI will be treated with a GLP-1 agonist. DIO3 expression will be measured. Heart morphology and function will be compared between groups.

Impact: Improved survival rates after MI is of critical importance. Our proposed investigation challenges current paradigms regarding TH's role and their metabolites in cardiac responses to MI. Our proposal tests the novel premise that DIO3 upregulation is necessary for better cardiac recovery after a MI event. This proposal has the potential to accelerate research in the cardiovascular field and lead to the discovery of new therapeutic options.

Marisa Stahl, MD (Special KL2 Supplement Award) 7/22/2020 - 4/30/2023
F / not URM
Assistant Professor
Pediatrics/Gastroenterology, Hepatology and Nutrition
Mentors: Joaquin Espinosa, PhD, Ron Sokol, MD, Edwin Liu, MD, & Jill Norris, PhD
Celiac disease signatures in Down syndrome

This project was related to an INCLUDE supplement for our parent CCTSI award.

Demetria McNeal Bolden, MBA, PhD (Diversity Supplement Award) 10/1/2021 –9/30/2023
F / URM
Assistant Professor
Cardiology
Mentors: Pamela Peterson, MD, MPH and Amy Huebschmann, MD
Understanding provider and patient factors which affect peripheral arterial disease management.

This project was related to a DIVERSITY supplement for our parent CCTSI award.

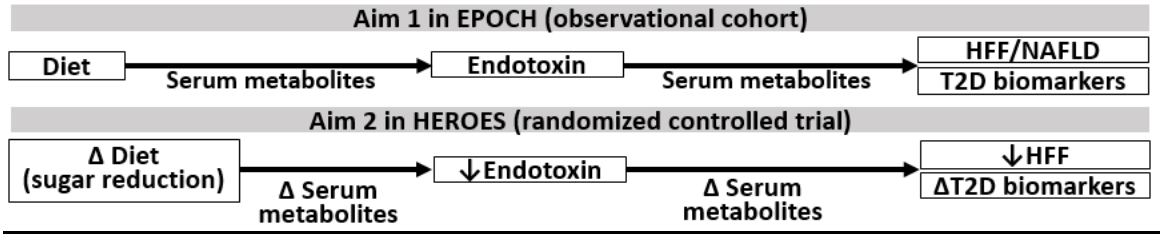
Wei Perng, PhD, MPH 2/1/2020 - 1/31/2023
F / not URM
Associate Professor
Epidemiology
Mentors: Dana Dabelea, MD, PhD & Deborah Glueck, PhD
Biomarkers and mechanisms of NAFLD and T2D pathogenesis in two adolescent cohorts

SPECIFIC AIMS
Non-alcoholic fatty liver disease (NAFLD) is on the rise children and adolescents, affecting 1 in 4 obese youth and up to 10% of the general pediatric population (1). While NAFLD has conventionally been viewed as a form of hepatic insulin resistance that co-exists with other leading metabolic diseases like type 2 diabetes

(T2D), increasing evidence in adults (2, 3) suggests that NAFLD may actually precede and promote development of T2D via proinflammatory and profibrotic pathways (4-7). Accordingly, identification of risk factors targeting prevention or reversal of NAFLD progression may have potential to ameliorate T2D, which has increased dramatically among young people in the U.S. and other developed nations over the last three decades (8).

One pathogenic mechanism implicated in both NAFLD (9-11) and T2D (7, 12) is bacterial translocation, or the passage of intestinal bacteria into circulation. A key study in rhesus macaques showed that short-term fructose consumption increased serum lipopolysaccharide (LPS), the active component of the intestinal bacterium endotoxin. Elevated LPS, in turn, promoted NAFLD progression independent of weight gain (13). Studies in humans have observed inverse relations of prudent dietary patterns (14, 15), and positive associations of sugar (16-18) and fat intake (19, 20) with serum endotoxin. In piecemeal fashion, researchers have also linked higher serum endotoxin to NAFLD progression/risk (21-26). Together, these studies indicate a specific effect of LPS on NAFLD progression/risk, and point toward diet as a modifiable risk factor. **Yet, human evidence is limited with respect to causal inference and prevention potential**. Causally, the direction of effects among diet, endotoxin, and NAFLD is unclear as no study has assessed all three components in the same population. From a prevention standpoint, the majority of existing studies focused on adults with advanced NAFLD, for whom prevention is limited given that end-stage liver disease is difficult – if not impossible – to reverse.

Figure 1 Conceptual model of research aims



In this proposal, we seek to improve causal inference, gain insight into mechanistic pathways, and identify avenues for prevention of NAFLD (as well as T2D, via its association with NAFLD), by leveraging: (1) an observational cohort of youth and (2) a randomized controlled trial of adolescents with NAFLD. Among 399 participants of **Exploring Perinatal Outcomes among Children (EPOCH)**, a multi-ethnic pediatric cohort with data and samples collected at age ~10 (T1) and 16 y (T2), including MRI- assessed hepatic fat fraction (HFF) at T2, we will investigate prospective associations of diet, endotoxin, HFF and change in key T2D risk biomarkers (fasting glucose, insulin, insulin resistance, disposition index); and identify novel mechanistic pathways via untargeted metabolomics profiling of fasting serum. Next, among 120 participants of the **Healthy Eating through Reduction of Excess Sugars (HEROES)** trial, we will examine the effect of sugar reduction on serum endotoxin, as well as the relation of change in endotoxin with change in HFF, T2D biomarkers, and key metabolites among obese Hispanic youth (12-18 y). Our **Specific Aims** are:

***Aim 1*. Observational study of diet, endotoxin, HFF, and T2D biomarkers in EPOCH. *We predict that*:**
a. A diet characterized by unhealthy fats (saturated, *trans*) and refined carbohydrates at T1 is associated with: **(i)** higher serum endotoxin, as indicated by LPS, LPS-binding protein, and human endotoxin core antibody IgG across T1 and T2; **(ii)** higher HFF at T2; and **(iii)** worsening T2D biomarkers between T1 and T2. We predict that higher serum endotoxin at T1 is associated with higher HFF T2, as well as worsening T2D biomarkers from T1 to T2, independent of conventional risk factors (body mass index, alanine aminotransferase, lipid profile). Serum endotoxin mediates the prospective relationship of diet with HFF and T2D biomarkers. Distinct sets of metabolites link diet to endotoxin, and endotoxin to HFF and T2D biomarkers; **(iv)** metabolomics findings in EPOCH will be validated among participants in the HEROES trial.

***Aim 2.* Effect of sugar reduction on endotoxin, HFF, and T2D biomarkers in HEROES. *We predict that*:**
a. (i) The sugar-reduction intervention will decrease serum endotoxin; **(ii)** decreased serum endotoxin will be associated with decreased HFF, improved T2D biomarkers, and changes to metabolites identified in Aim 1.
b. The effect of the sugar-reduction intervention on HFF and T2D biomarkers will be mediated by decreased serum endotoxin.

Impact: Achievement of our aims will not only improve understanding of NAFLD pathogenesis during a vulnerable life stage for development of metabolic disease (27), but will also translate to identification of novel

and inexpensive biomarkers that may be used in a clinical setting, and inform prevention strategies that will aid in prevention of NAFLD and T2D in children and adolescents.

Bradley Haverkos, MD, MPH 12/1/2019 - 1/30/2022
M / not URM
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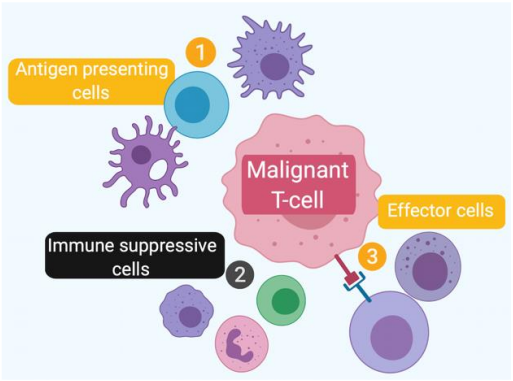
Medicine/ Hematology_Blood & Marrow Transplant
Mentors: Eduardo Davila, PhD & Craig Jordan, PhD
Leveraging immunotherapy to improve treatments for newly diagnosed peripheral T-cell lymphomas

SPECIFIC AIMS: The long-term goal of this project is to identify optimal ways to utilize immunotherapeutic approaches to improve treatment outcomes for patients with peripheral T-cell lymphomas (PTCLs). PTCLs are a heterogeneous category of non-Hodgkin lymphomas. The combination cytotoxic chemotherapy regimen dose adjusted (DA)-EPOCH (etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide) is a first line treatment option for patients with PTCL, but for most PTCL subtypes relapses are common and long-term outcomes are poor, with 5-year survival of 20-30%. Therapies that improve outcomes for newly diagnosed PTCLs are needed. Checkpoint blockade (CPB) is an immunotherapeutic approach that has shown efficacy as a single agent in heavily pre-treated PTCL patients. Studies suggest that ineffective antigen presentation, a pro- tumor microenvironment, and an absent T-effector cell response predict resistance to CPB, although none have been tested in PTCL. Preclinically, the addition of cytotoxic chemotherapy to CPB can overcome these resistance mechanisms and thereby improve clinical efficacy. However, it is critical that we mechanistically understand the immunologic impact of CPB + EPOCH in vivo so that we can predict response/resistance and guide future treatment. Our overarching hypothesis is that CPB +

EPOCH will promote effective antigen presentation, an anti-tumor microenvironment, and a T-effector response by 1) increasing major histocompatibility complex, 2) depleting immune suppressive cells, and 3) increasing effector cells leading to a more robust interferon gamma response. To test this approach clinically, we are conducting a multi-center phase I/II clinical trial using DA-EPOCH in combination with nivolumab (a monoclonal antibody blocking the programmed death 1 checkpoint) for the first-line treatment of PTCLs. We will test our hypothesis using tumor tissue and blood sampled pre and post treatment from three treatment groups (EPOCH + nivolumab, EPOCH, and single agent CPB), evaluating the following specific aims:



Aim 1: Determine propensity of EPOCH with and without nivolumab to promote immune recognition and T-cell activation. Hypothesis: *EPOCH will increase Major Histocompatibility Complex (MHC) on malignant cells and bystander macrophages, and blocking the Programmed Death 1 (PD-1) checkpoint will increase T-cell activation further increasing MHC I through interferon gamma production.* Using specimens from our three treatment cohorts, we will measure expression of MHC complexes I and II on malignant cells and neighboring antigen presenting cells (i.e. macrophages, dendritic cells, and B-cells), with multiplex immunofluorescent immunohistochemistry on tumor tissue from the diagnostic biopsy site before and after treatment. We will then assess spatial arrangements of tumor infiltrating lymphocytes and antigen presenting cells to evaluate the possibility for a tumor specific T-cell response. Lastly, we will measure quantitative and qualitative T-cell responses in peripheral blood by flow cytometric analysis. Collectively, these investigations will establish a new paradigm whereby EPOCH primes for a tumor specific T-cell response, which can be enhanced with nivolumab.

Aim 2: Establish the ability of EPOCH to reshape the tumor environment towards one that supports tumor immunity. Hypothesis: *Since doxorubicin and cyclophosphamide abrogate myeloid derived suppressor cells (MDSCs) and T-regulatory cells (Tregs) respectively, we hypothesize that EPOCH will deplete immune suppressive cells in the tumor microenvironment, whereas nivolumab will not affect the surrounding immune suppressive cells.* Using specimens from our three treatment cohorts, we will quantify the frequency, spatial distribution, and phenotype of immune suppressive cells (i.e. Tregs, MDSCs, and tumor associated

macrophages) in the tumor microenvironment, with multiplex immunofluorescent immunohistochemistry on tumor tissue from the diagnostic biopsy site before and after treatment. We will also quantify immune suppressive cells in peripheral blood by flow cytometric analysis. These investigations will demonstrate the influence of EPOCH on the negative regulators of an immune response within the tumor environment.

Impact: This project will provide a mechanistic rationale to use EPOCH in combination with checkpoint blockade. Ultimately, these discoveries will lead to a novel improved immunotherapeutic treatment approach for newly diagnosed PTCL patients. Further, this model using CPB + cytotoxic chemotherapy studied across multiple lymphoma subtypes in settings, where CPB is currently being studied.

Michelle H. Leppert, MD 12/1/2019 - 2/28/2023
F / not URM
Assistant Professor
Neurology
Mentors: P. Michael Ho, MD, PhD & Cathy Bradley, PhD
Sex Disparities in Young Adult Strokes

Specific Aims: More than 120,000 young adults, under 50 years old, will have a stroke in the U.S. this year. Young adults with stroke have a 3 times higher rate of mortality and 2 to 3 times higher rate of unemployment compared to their peers.Furthermore, young women with strokes have 2 to 3 times worse functional outcomes compared to young men. This is a growing problem, as young adult stroke admissions rose 40% in the past decade and the average age of first time strokes continues to decline.Our recent study in a large U.S. cohort, was one of the first to demonstrate that incident stroke claims in young adults 25 to 44 is higher in women than men. This observation challenges the assumption that strokes in young adults are largely the result of cardiovascular risk factors, as these factors are less common in women. However, we still do not understand differences in the etiology of stroke between young men and women and consequently why women have poorer outcomes.

Non-cardiovascular risk factors may be stronger drivers of strokes in young women. Compared to men, young women with strokes have a lower prevalence of hyperlipidemia, smoking, and coronary artery disease. Meanwhile, non-cardiovascular risk factors including pregnancy, oral contraceptive pill (OCPs) use, and migraine with aura have been raised as possible factors associated with strokes in young women. We do not understand if these sex specific risk factors lead to a predilection for certain stroke types (i.e. large vessel occlusions due to the thromboembolic risk of OCPs). Further, it is unclear if the poorer functional outcomes in women with stroke are due to more severe strokes or a higher risk of recurrent strokes. Without addressing these sex-related risk factors, current prevention efforts focused on modifying cardiovascular risk factors may do little to curb the incidence of strokes in young women.

Currently there are no large clinical cohort studies of young adult strokes in the US to understand how different risk factors influence the development of strokes and their longer-term outcomes. Low enrollment numbers, lack of a control group, and/or lack of clinical data (such as stroke severity or type) have limited prior studies of young adult stroke. We will address these prior limitations by leveraging two unique data sources. The Colorado's All Payer's Claims Database (CO-APCD) contains 80% of insured Coloradoans with both commercial and Medicaid insurance. This database will allow us to follow a large population of young adults and compare risk factors in those with (approximately 3000 to 4000 young adult strokes) and without strokes. For a subset of patients hospitalized at 27 hospitals in Colorado (including all stroke centers), we will link the CO-APCD to the Get With The Guidelines (GWTG) stroke registry containing detailed clinical information about each stroke admission. Using this in depth, linked database we will be able to assess how pre-stroke risk factors may have contributed to different stroke types and severity among young men and women.

My goal is to become an independent physician investigator focused on understanding why young adults have strokes and then translate these findings into strategies for intervention and prevention. The CCTSI K12 Program will be pivotal for my education in translational sciences in addition to providing an important stepping stone toward obtaining a NIH mentored career development award. In my future career

development award, I will expand the linked database of young strokes into other states and translate our findings into public health efforts to reduce young adult strokes in Colorado.

Aim 1: Using a case-control study design, compare the association of cardiovascular and non-cardiovascular risk factors among young adult women and young adult men with stroke to those without stroke matched by sex, age, and geographic region in the CO-APCD.
H1: Cardiovascular risk factors (e.g. hypertension, hyperlipidemia) are associated with higher stroke risk in young men than young women.
H2: In young women, non-cardiovascular risk factors (e.g. migraine, renal insufficiency, HIV, antiphospholipid syndrome, pregnancy, history of pre-eclampsia or eclampsia, and oral contraceptives) are associated with higher risk of stroke compared to traditional cardiovascular risk factors.

Aim 2: Assess for sex differences in first time stroke types (e.g. hemorrhagic, ischemic: large vessel occlusion, small-vessel occlusion, cardioembolism, stroke of other determined etiology, and stroke of undetermined etiology), severity, and longitudinal outcomes (e.g. recurrent stroke) using the GWTG linked with CO-APCD. H1: Compared to young men with stroke, young women will have a higher rate of large vessel occlusions**.**
H2: Compared to young men with stroke, young women will have a higher rate of poor longitudinal outcomes.

KL2/K12 "Like" Scholars (Supported by Children's Hospital with Institutional Funding)

Caroline Hall, MD, PhD* 12/1/2019-11/30/2022
F / not URM
Assistant Professor
Pediatrics/Gastroenterology, Hepatology & Nutrition
Mentors: Sean Colgan, PhD & Edwin de Zoeten, MD,PhD
Creatine uptake regulates barrier function and disease activity in IBD

Statement of purpose and specific aims

The inflammatory bowel diseases (IBD) are multifactorial diseases with contributions from genetics, environment, microbiome and host immune system. Current therapies for IBD, including Crohn's disease and ulcerative colitis (UC), are often inadequate with lack of response to therapy and harmful side effects. The implications of these side effects are most significant for children who have longer lifetime medication exposure. *The goal of this proposal is to identify safe therapeutic options centered around tissue energetics.*

In work leading up to this proposal, we identified a prominent role for the energetic metabolite creatine in the regulation of mucosal inflammation. A key component of intestinal immune regulation is maintenance of a selectively permeable epithelial barrier. Barrier maintenance is an energy dependent process. Creatine is a key regulator of energy allocation in the cell. There is one known creatine transporter, CrT (or SLC6A8), which allows for creatine uptake. There are no prior studies examining the regulation of CrT in epithelial cells.

The creatine pathway has been implicated in intestinal mucosa homeostasis in a number of different studies including work from our lab that identified a protective role for creatine supplementation in mouse models of colitis and that creatine machinery was inducible by hypoxia (Glover et al PNAS 2013). Additionally, a study screening for susceptibility to colitis identified that loss of GAMT, an enzyme necessary for endogenous creatine production, increased susceptibility (Turer et al PNAS 2017). Creatine is an attractive therapeutic option with a long safety record for all ages.

With this evidence, we have focused on the feasibility of creatine as a therapy for IBD patients. We identified wide variability in the expression of the CrT in patient biopsy samples with significantly less CrT in IBD patients compared to controls. We hypothesized that inadequate CrT would result in failure of IBD patients to respond to supplementation. In order to evaluate this concern, we investigated the role of CrT in intestinal epithelial cells (IECs). Using loss and gain of CrT function in IECs, we have revealed that CrT expression in IEC lines has a direct and significant impact on barrier formation as measured by transepithelial electrical resistance and FITC-dextran flux assay as well as wound healing. The IEC CrT knockdown cells express a leaky tight junction profile as well as irregular localization of tight junction proteins which likely contributes to the profound barrier disruption.

Based on these initial findings, *our global hypothesis is that creatine transport is central to mucosal integrity and has a significant impact on intestinal epithelial barrier formation and development of IBD*. We believe that regulation of the creatine system and creatine supplementation hold potential in therapeutic management of IBD. Three specific aims are directed at testing this hypothesis*:*

Specific Aim 1: Elucidate mechanisms of CrT regulation.
Hypothesis: Hypoxia and HIF induce expression and activity of the CrT in IECs and enteroids that can be pharmacologically regulated by HIF stabilizing agents (i.e. prolyl hydroxylase inhibitors).

Specific Aim 2: Define the role of CrT in the epithelium in murine colitis and ileitis models.
Hypothesis: Transgenic $CrT^{Flox}Villin^{Cre}$ *mice lacking intestinal epithelial CrT will have increased susceptibility to models of colitis due to energy-dependent barrier dysfunction. Also, creatine supplementation is protective in TNF-alpha ARE ileitis model.*

Specific Aim 3: Determine the role of CrT expression and function in IBD patient biopsies.
Hypothesis: In patient intestinal samples, CrT expression correlates with intracellular creatine and inversely correlates with disease activity.

The overall goal of this proposal is to define the contribution of creatine and creatine transport to mucosal homeostasis in health and during active inflammation. It is our hope that a better understanding of this pathway might result in strategies that could be used for therapeutic purposes in IBD.

Jillian Cotter, MD, MSCS* 12/1/2021 – Current
F / not URM
Assistant Professor
Pediatrics/Hospital Medicine
Mentors: Samuel Dominguez, MD, PhD & Lilliam Ambroggio, PhD
Reducing Antibiotic Overuse in Pediatric Pneumonia

Specific Aims

Community acquired pneumonia (CAP) is the fifth most common diagnosis among hospitalized children with over 125,000 admissions annually. Despite this large burden, no findings reliably distinguish bacterial CAP, which requires antibiotics, from viral CAP, which does not. Unlike adults, most pediatric CAP is likely viral. In the largest study of CAP etiology in hospitalized children, over 70% had viruses and only 15% had bacterial pathogens identified, yet 88% received antibiotics. This discrepancy highlights antibiotic overuse and problems with current prescribing practices. Unnecessary antibiotics place children at risk for adverse events and side effects without benefits. They are also a major concern worldwide given rising antibiotic resistance. Antibiotic- resistant bacteria cause >2.8 million infections, 35,000 deaths, and cost $55 billion annually.**Thus, there is a significant need to reduce antibiotic overuse in pediatric CAP.**

To successfully reduce unnecessary antibiotics, we first need to identify children who do not benefit from treatment (Aim 1). We will compare outcomes between matched patients who differ only by antibiotic status; those with similar outcomes, regardless of antibiotic use, are likely low risk for bacterial CAP and could safely be managed without them. Length of stay is our primary outcome given that it represents time to clinical improvement and is clinically significant to families, clinicians, and hospitals. A study of >300 children with suspected CAP in an Emergency Department (ED) found no difference in treatment failure or quality-of-life measures between those who did and did not receive antibiotics, suggesting there are opportunities to safely reduce antibiotic use in the ambulatory setting. No similar studies have been performed in the inpatient setting. Given the unique opportunity for continued monitoring of hospitalized children, this is an ideal cohort for antibiotic de-implementation. From prior studies, we hypothesize that children with negative (no evidence of CAP) or equivocal ("atelectasis vs pneumonia") chest radiographs (CXR) are low risk. We will also explore factors such as age and illness severity to identify a low risk cohort in which we can safely defer antibiotics.

Effectively reducing unnecessary antibiotics also requires identifying modifiable factors that drive antibiotic use (Aim 2). We will explore potential factors associated with inpatient antibiotic use, such as CXR findings, age, and illness severity. We will focus on treatment momentum, the tendency to continue antibiotics

in the inpatient setting that were started in the ED, as a potential novel and understudied driver of antibiotic overuse. In pilot data from my mentor's single site prospective cohort of children hospitalized with CAP, 89% of patients who received antibiotics in the ED had them continued as an inpatient, *including 70% of children with a negative CXR.* Given these concerning single site findings, additional multicenter data are needed to understand the utility of targeting treatment momentum in future stewardship interventions.

In collaboration with the Pediatric Research in Inpatient Settings (PRIS) network, which has extensive experience with multicenter studies, and four children's hospitals, which have committed to this project, we propose a multicenter retrospective study of children hospitalized with CAP. We will use linked data from two complementary data sources - Pediatric Health Information System (PHIS), a national administrative database of children's hospitals, and chart review, to achieve the following *specific aims:*

Aim 1. Determine the association between inpatient antibiotic use and length of stay and secondary outcomes for children hospitalized with CAP. We will use propensity score matching to match patients who differ only by antibiotic status and assess clinical outcomes with regression analysis.
Hypothesis 1: Among children with negative and equivocal CXRs, clinical outcomes are similar between those who receive antibiotics and those who do not.

Aim 2. Evaluate whether antibiotic initiation in the ED is associated with continued inpatient antibiotic use among children hospitalized with CAP. We will perform multivariable logistic regression to identify factors that are associated with inpatient antibiotic use.
Hypothesis 2: Receipt of antibiotics in the ED is independently associated with inpatient antibiotic use, after adjusting for covariates (e.g., CXR findings).

These aims will help us understand opportunities for safely reducing antibiotics in the inpatient setting, diagnose low risk cohorts, and identify modifiable factors to target for future interventions. This pilot data will support my *immediate next steps* in a K23 application *prospectively* exploring the impact of deferring antibiotics in low risk patients and qualitatively evaluating additional clinical and systems factors that drive antibiotic overuse in these low risk cohorts. Ultimately, this will allow me to accomplish my *long-term career goal* of becoming an independently funded researcher dedicated to improving outcomes for children with common, serious infections through the dissemination and implementation of evidence-based stewardship interventions.

Jose Diaz-Miron, MD* 12/01/2023 – Current
M / URM
Assistant Professor
Pediatrics/Surgery
Mentors: Tell Bennett, MD & Lisa DeCamp, MD
Understanding variation and clinical factors associated with the use of extracorporeal cardiopulmonary resuscitation in children

SPECIFIC AIMS
Extracorporeal cardiopulmonary resuscitation is a modality whereby venous and arterial cannulas are inserted through a neck incision to provide hemodynamic and respiratory support during active cardiopulmonary resuscitation (CPR). While most critically ill patients are placed on extracorporeal membrane oxygenation (ECMO) during periods of relative hemodynamic stability, ECPR accounts for 10% of pediatric ECMO cannulations. The evidence to support the use of ECPR for non-cardiac conditions (e.g.: sepsis, pulmonary hypertensive crises, respiratory failure, and others) is judged to be low quality, and the situations in which surgeons and medical teams utilize ECPR are poorly understood. Under ideal circumstances, pediatric surgical interventions typically involve extensive discussion with family members and care providers about operative risks and benefits. Unfortunately, pediatric surgeons are asked to consider ECPR in patients who have acutely decompensated and require CPR, greatly diminishing the available time for high-quality decision-making. **Early identification of patients with non-cardiac conditions that may benefit from ECPR prior to arrest is needed.** There is a critical need to understand current factors influencing use of ECPR and to document situations in which ECPR has the most benefit for the patient. Once documented and factors associated with positive ECPR outcomes are identified, a clinical decision support (CDS) tool can be developed to enable medical teams and families to make more informed decisions.

My *long-term goal* is to become a national leader in the development of objective criteria for evaluation of surgical interventions of uncertain benefit, such as ECPR, to understand variation in their use, and use this

information to develop tools to better support surgeons and other clinicians facing difficult acute clinical decisions. This career development application will allow me to develop and master the skills needed through practical application and dedicated mentorship by experts in the field.

Based on my clinical experience at different institutions and studies demonstrating surgical variation with use of end-of-life procedures,[3] my *overarching hypothesis* is that significant variation across centers and providers in the use of ECPR exists and is largely driven by institutional culture, timely access to ECPR, prior experiences, and/or emotional considerations. Further, I hypothesize that tools to identify children at risk for cardiac arrest earlier can accelerate decisions so that they occur in less emergent conditions. I seek to test these hypotheses through the following *specific aims*: **Evaluate factors associated with ECPR outcomes.** My *working hypothesis* is that variables including proceduralist training specialty, timing to cannulation, and reason for decompensation are associated with patient outcomes including survival, neurologic complications, and total CPR time. To test this hypothesis, I plan to conduct a retrospective cohort study of electronic health records at four diverse children's hospitals.

1. Conduct a decisional needs assessment to identify factors influencing the use of ECPR. A decisional needs assessment[4] will document factors that influence decision-making to use or not use ECPR. The decisional needs assessment will focus on drivers and detractors for ECPR, the importance of a timely evaluation and cannulation for ECPR, the use of predictive tools in ECPR scenarios, and the emotional toll associated with these procedures. My *working hypothesis* is that acceptance of pediatric ECPR as a valuable tool will be highly variable among medical providers and organizations. Some of the evaluated institutional and clinical factors for ECPR use will include institutional culture, access, training, procedural practices, and provider perceptions. This aim will be evaluated using the Ottawa Decision Support Framework through semi-structured interviews among identified stakeholders including intensivists, proceduralists, ancillary staff, and parents.

2. Develop and validate a statistical model for survival after ECPR cannulations. My *working hypothesis* is that a predictive statistical model from the data gathered in SA 1 can be constructed and used to predict survival, and thus, which patients benefit most from ECPR. Hence, we will use those multi-center data to develop and validate a model on the identified site patients to predict ECPR survival. We will consider traditional multiple logistic regression modeling with a binary outcome of survival, as well as survival analysis models to account for the time-to-event nature of the data (e.g., Cox proportional hazards models) and random survival forests, a machine learning ensemble method, for the best ability to predict survival after ECPR.

At the completion of the proposed aims, the knowledge gained will be transferable to many other situations faced by pediatric surgeons where an intervention may be of uncertain benefit such as laparotomies, oncologic procedures, and emergent operations in the trauma bay. The proposed project will allow me to develop skills in evaluating individual, inter- and intra-institutional practice variations, qualitative analysis, and the use of predictive tools to assist in decision-making. The important lessons from this study will then serve as the basis for a future R01 testing a generated CDS tool informed through SA 2 in prospective clinical practice.

T32 Post-Doctoral Program RPPR- Progress Report

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

The CCTSI Post-Doctoral Program's goal is to meet the needs of the CTSR community by preparing diverse interdisciplinary translational scientists that are team-oriented and have developed characteristics and associated competencies necessary for successful CTSR careers. To accomplish our overall goal, the following program objectives will be met:

1. Attract, recruit and retain diverse trainees by demonstrating that Diversity Accelerates Research and Translation (DART) is a core program value and commitment.
2. Promote trainee development of foundational characteristics of Translational Scientists: Domain Expert, Rigorous Researcher, Boundary Crosser, Process Innovator, Team Player, Skilled Communicator, and Systems Thinker, and in doing so, enhance the overall scientific community.
3. Apply evidence informed mentoring practices to support developing trainees from all backgrounds for career persistence and success in CTSR.
4. Develop trainees' knowledge, skills and abilities to conduct research in diagnostics, therapeutics, clinical interventions, and behavioral modifications that improve health.
5. Support study conduct concordant with ethical and regulatory principles through required training in research ethics, RCR, GCP, regulatory compliance, rigor and reproducibility, diversity, equity and inclusion and data science principles.
6. Develop trainee's ability to communicate effectively (writing, speaking and listening) with diverse stakeholder groups.
7. Engage trainees with a new translational community and network that brings new insights, perspectives, and skills through immersion experiences with translational mentors.
8. Approach CTSR as a team endeavor and foster trainees' teaming and leading skills for high performing teams.
9. Apply the One Health Framework to culminate the integration of translational scientist competencies.
10. Identify, monitor, track, review and respond to, as necessary, indicators and metrics of an effective and successful program through continuous quality improvement.

B.1.a Have the major goals changed since the initial competing award or previous report? No, they did not change.

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS

The program was able to mount the CCTSI T32 Post-Doctoral program very quickly. We were informed at the end of August 2023 that we would be funded in September 2023 and were able to start the program October 2023. We identified a major challenge to the program was the grant start date. Clinical post-doctoral awardees that are part of a graduate degree program typically start in the summer and not in October. It became very evident from speaking with potential applicants and program directors of programs that form our CCTSI T32 Post-Doctoral program pool that this timing would interfere with trainees timing and requirements, especially requirements for physician specialties. We received two high quality applications, one from a veterinarian with a PhD who is completing a master's in clinical science and the other from a surgical resident completing a PhD in Clinical Investigation-Clinical Science. Both applicants were awarded but this left two unfilled slots. To address the timing obstacle, we worked with the Dr. Conroy to identify a path to having the award with a July start date instead of a September start date. Because of the 2 open slots, a spring competition is being held and will identify 2 post-doctoral clinicians to start July 2024 for two-years. The RFA was released and distributed to all program directors the end of December 2023 with email blasts sent every two weeks through March.

Both awardees completed an Individualized Career Development Plan (ICDP) with their mentors and presented it to their peers and T32 faculty for feedback, guidance and encouragement. All ICDPs are reviewed to ensure that training in RCR, GCP will occur and that trainees have completed an ethics and responsible conduct of research course or will be completing the course this AY23-24. This helps build competencies for a rigorous researcher. The ICDP of each awardee was reviewed to ensure that training and career development activities were planned and resources available to develop competencies for the following Translational Scientist characteristics: Boundary Crosser, Process Innovator, Team Player, Skilled Communicator, and Systems Thinker. These activities address Objectives 2, 4, 5.

To accomplish Objective 3, both trainees and their research mentors completed a baseline mentoring relationship survey that involves the mentor providing judgements regarding their mentee and self-assessments of their own activities and skills. Likewise, the mentee provides judgements regarding their mentor and self-assessments of their own activities and skills. This survey is completed again close to the one-year point and at the end of the program. The mentor-mentee dyad's data will be reviewed to identify struggling relationships with follow-up and support provided by the program directors. Additionally, to support this objective, Mentoring^3: Mentor, Mentee and Peers, a program for mentees and mentors to develop skills and apply strategies for effective mentoring relationships was developed this year. Both mentors and mentees attend workshops as a dyad and separately in groups of mentors and mentees. Mentors and mentees completed 10 hours of workshops by the end of Spring 2024.

To support Objective 6, post-doctoral trainees completed the CCTSI program, Effectively Communicating your Research to the Public, in November/December 2023. The program includes participation in 3 workshops that focuses on storytelling, developing and delivering your pitch, and building and managing your social media presence.

Both trainees average 8-10 hours per month working with their translational mentor in their immersion community. This activity addresses Objective 7. The surgical awardee is completing his immersion experience at CSU School of Veterinary Medicine with a veterinarian specializing in cardiac imaging. The veterinarian is completing her immersion experience to gain insight into running and managing human randomized clinical trials and biospecimen repositories. Awardees report that these immersion experiences are going well and that their translational

mentors are engaged and interested in their development and research, as evidence as serving as a PhD thesis committee member.

To support the ability of trainees to develop skills for leading high performing teams (Objective 8), all awardees completed the CCTSI Teaming and Leading program.

Doug Thamm, a program director, provided a seminar during one of our T32 seminars on One Health to support Objective 9. Additionally, during our T32 seminars, teams applying the OneHealth framework are presenting their work and sharing lessons learned.

Our CCTSI T32 program is applying the principles of continuous quality improvement to inform the need for revision and the types of changes/additions necessary. Awardees completed baseline assessments related to their clinical and translational research competencies/skills and possession of translational scientist characteristics. Additionally, awardees complete evaluations following participation in a CCTSI program so that our program can be improved and address learners' needs.

B: What do you plan to do during the next reporting period to accomplish your goals?

- Expand and revise our marketing and recruitment by providing personalized communication to program directors.
- Provide our newly developed, Mentoring^3: Mentors, Mentee, Peers program, to awardees earlier in the program. It was delayed this year while we developed the curriculum/program.
- Review the mentee-mentor assessment data across baseline and 1 year timepoints to gauge the quality of relationships, identify dyads needing attention and to identify gaps in our programming.
- Organize, provide and evaluate our community Café Scientifique events where post-doctoral trainees present their research to community members/general public.
- Revise the newly developed Mentoring^3: Mentors, Mentee, Peers program based on evaluation of pilot offering. Provide broader dissemination of the newly developed Mentoring^3: Mentors, Mentee, Peers to include post-doctoral fellows across partnering communities. Develop and pilot the train the trainer type of program to increase the number of program faculty for Mentoring^3 and include faculty across our CCTSI partnering communities.
- Develop and provide a Writing Accountability Group (WAG) to support manuscript development and grant development of our post-doctoral trainees.
- Evaluate the event/opportunity for trainees to meet with the CCTSI Post-Doctoral T32 Program's Internal Advisory Committee members to receive guidance and feedback on their careers and research.
- Revise Teaming and Leading program regarding the newly added content to support leadership skill development based on feedback/evaluation of post-doctoral trainees.
- Integrate One Health into the post-doctoral trainees' presentations and push them to identify important aspects of translational clinician scientists and important bottlenecks to address in clinical and translational science and research.
- Continue to offer and revise/improve our programs through ongoing evaluation.

E2: What is the impact on physical, institutional, or information resources that form infrastructure?

The program, *Mentoring^3: Mentors, Mentees, Peers*, was developed, and its provision expanded to meet the needs of post-doctoral fellows and their mentors.

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST? (Not applicable for most T32s).

Nothing to Report

G2: Responsible Conduct of Research

Awardees are required to complete an ethics and responsible conduct of research graduate course (≥ 15 hrs of instruction and discussion) during their training/degree. If awardees have not completed an ethics and responsible conduct of research course that included Good Clinical Practice prior to starting the CCTSI T32 program, they are required to complete a course during the first year of the award. If awardees were not taking an approved graduate level course during the time of the award, they participated in regularly scheduled Zoom workshops offered/organized through the CU Anschutz Medical Campus, which meets NIH requirements. Lisa Cicutto, the T32 Program Director, participates in these offerings by providing workshops on mentoring relationships: roles and responsibilities of mentors and mentees in collaborative research.

T32 Pre-Doctoral Program RPPR- Progress Report

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

The overall goal of our Pre-doctoral program is to meet the needs of the translational science and research community by preparing diverse inter-disciplinary doctoral trainees that are team-oriented and have developed characteristics and associated skills necessary for successful Clinical and Translational Science and Research (CTSR) careers. To accomplish this, the following program objectives will be met:

1. Attract, recruit and retain diverse trainees by demonstrating that Diversity Accelerates Research and Translation (DART) is a core value and program commitment.
2. Promote trainee development of foundational characteristics of Translational Scientists: Rigorous Researcher, Boundary Crosser, Process Innovator, Team Player, Skilled Communicator, and Systems Thinker.
3. Apply evidence informed mentoring practices to support developing trainees from all backgrounds for career persistence and success in CTSR.
4. Develop trainees' knowledge, skills and abilities to advance CTSR in diagnostics, therapeutics, clinical interventions, and behavioral modifications.
5. Support study conduct concordant with ethical and regulatory principles through required training in ethics, RCR, GCP, regulatory compliance, rigor and reproducibility and data science principles.
6. Develop trainee's ability to communicate effectively (oral and written) to diverse stakeholder groups.
7. Engage trainees with a new translational community and network that brings new insights, perspectives, and skills through immersion experiences with translational mentors.
8. Approach clinical and translational science and research as a team endeavor and foster trainees' teaming and leading skills for high performing teams.
9. Identify, monitor, track, review and respond to, as necessary, indicators and metrics of an effective and successful program through continuous quality improvement.

B.1.a Have the major goals changed since the initial competing award or previous report? No, they did not change.

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS

The program was able to mount the program very quickly. We were informed at the end of August 2023 that we would be funded in September 2023 and were able to start the program October 2023 with all 8 pre-doctoral slots awarded. This includes one medical student completing a one-year award. The remaining 7 awardees are in PhD programs and completing the program for two-years. We received 18 applications of which 7 were from populations that are typically under-represented. Of the awardees, 50% of trainees are from populations typically under-represented. Awardees represent the following disciplines: medical student, public health-epidemiology, microbiology, cancer biology, neuroscience and bioengineering.

All awardees completed an Individualized Career Development Plan (ICDP) with their mentors and presented it to their peers and T32 faculty for feedback, guidance and encouragement. All ICDPs are reviewed to ensure that training in RCR, GCP will occur and that trainees have completed an ethics and responsible conduct of research course or will be completing the course this AY23-24. This helps build competencies for a rigorous researcher. The ICDP of each awardee was reviewed to ensure that training and career development activities were planned and resources available to develop competencies for the following Translational Scientist characteristics: Boundary Crosser, Process Innovator, Team Player, Skilled Communicator, and Systems Thinker. These activities address Objectives 2, 4, 5.

To accomplish Objective 3, all trainees and their research mentors completed a baseline mentoring relationship survey that involves the mentor providing judgements regarding their mentee and self-assessments of their own activities and skills. Likewise, the mentee provides judgements regarding their mentor and self-assessments of their own activities and skills. This survey is completed again close to the one-year point and at the end of the program. The mentor-mentee dyad's data will be reviewed to identify struggling relationships with follow-up and support provided by the program directors. Additionally, to support this objective, Mentoring^3: Mentor, Mentee and Peers, a program for mentees and mentors to develop skills and apply strategies for effective mentoring relationships was developed this year. Both mentors and mentees attend workshops as a dyad and separately in groups of mentors and mentees. Mentors and mentees completed 10 hours of workshops by the end of Spring 2024.

To support Objective 6, all trainees completed the CCTSI program, Effectively Communicating your Research to the Public, in November/December 2023. The program includes participation in 3 workshops that focuses on storytelling, developing and delivering your pitch, and building and managing your social media presence.

All trainees average 8-10 hours per month working with their translational mentor in their immersion community. This activity addresses Objective 7. Awardees report that these immersion experiences are going well and that their translational mentors are engaged and interested in their development and research, as evidence as serving as a PhD thesis committee member.

To support the ability of trainees to develop skills for leading high performing teams (Objective 8), all awardees completed the CCTSI Teaming and Leading program.

Our CCTSI T32 program is applying the principles of continuous quality improvement to inform the need for revision and the types of changes/additions necessary. Awardees completed baseline assessments related to their clinical and translational research competencies/skills and possession of translational scientist characteristics. Additionally, awardees complete evaluations following participation in a CCTSI program so that our program can be improved and address learners' needs.

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

As mentioned above 100% of awardees developed and revised Individualized Career Development Plans to identify coursework, short courses/programs and immersion experiences to tailor their training and professional development. Individualized Career Development Plans are developed jointly with the awardees research mentor and their mentoring advisory team.

Individualized Career Development Plans (ICDPs) are at the beginning of the award year to obtain input into identified goals, courses and offerings to take advantage of during the award year, at the end of year one to share revisions, successes, discuss challenges and gain input, and then at the end of the award period to share accomplishments and lessons learned and to discuss future goals and activities. In addition to the tailored individualized education and training, CCTSI T32 awardees participate in CCTSI T32 seminars to receive additional career development. Topics that were addressed this year included developing and using ICDPs, what is a Clinical and Translational Scientist, tips for manuscript writing and a Writing Accountability Group, Shared Animal Models for Clinical and Translational Research conducted as Teams: Real life examples, the 3-minute thesis, and Rigor and Reproducibility.

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST? (Not applicable for most T32s).

Nothing to Report

B: What do you plan to do during the next reporting period to accomplish your goals?

- Expand and revise our marketing and recruitment by providing personalized communication to program directors.
- Provide our newly developed, Mentoring^3: Mentors, Mentee, Peers program, to awardees earlier in the program. It was delayed this year while we developed the curriculum/program.
- Review the mentee-mentor assessment data across baseline and 1 year timepoints to gauge the quality of relationships, identify dyads needing attention and to identify gaps in our programming.
- Organize, provide and evaluate our community Café Scientifique events where trainees present their research to community members/general public.
- Revise the newly developed Mentoring^3: Mentors, Mentee, Peers program based on evaluation of pilot offering. Broader dissemination of the newly developed Mentoring^3: Mentors, Mentee, Peers to all T32 programs. Develop and pilot train the trainer type of program to increase the number of program faculty for Mentoring^3.
- Develop and provide a Writing Accountability Group (WAG) to support manuscript development.
- Evaluate the event/opportunity for trainees to meet with the CCTSI Pre-Doctoral T32 Program's Internal Advisory Committee members to receive guidance and feedback on their careers and research.
- Revise Teaming and Leading program regarding the newly added content to support leadership skill development based on feedback/evaluation of trainees.
- Continue to offer and revise/improve our programs through ongoing evaluation.

E2: What is the impact on physical, institutional, or information resources that form infrastructure?

The program, *Mentoring^3: Mentors, Mentees, Peers*, was developed, and its provision expanded to meet the needs of other T32 programs and pre-doctoral programs.

G2: Responsible Conduct of Research

Awardees are required to complete an ethics and responsible conduct of research graduate course (≥ 15 hrs of instruction and discussion) during their training/degree. If awardees have not completed an ethics and responsible conduct of research course that included Good Clinical Practice prior to starting the CCTSI T32 program, they are required to complete a course during the first year of the award. If awardees were not taking an approved graduate level course during the time of the award, they participated in regularly scheduled Zoom workshops offered/organized through the CU Anschutz Medical Campus, which meets NIH requirements. Lisa Cicutto, the T32 Program Director, participates in these offerings by providing workshops on mentoring relationships: roles and responsibilities of mentors and mentees in collaborative research.