

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

			3. DATE RECEIVED BY STATE	State Application Identifier
			4.a. Federal Identifier	
<input type="radio"/> Pre-application <input checked="" type="radio"/> Application <input type="radio"/> Changed/Corrected Application		b. Agency Routing Number		
2. DATE SUBMITTED 2023-11-17	Application Identifier 234701	c. Previous Grants.gov Tracking Number		
5. APPLICANT INFORMATION			UEI*: YNT8TCJH8FQ8	
<p>Legal Name*: Joan and Sanford I Weill Medical College Department: Pediatrics Division: None Street1*: Weill Cornell Medical College Street2: 1300 York Avenue City*: New York County: New York State*: NY: New York Province: Country*: USA: UNITED STATES ZIP / Postal Code*: 10065-4805</p>				
<p>Person to be contacted on matters involving this application Prefix: First Name*: Aleta Middle Name: R. Last Name*: Gunsul Suffix: Position>Title: Exec Dir, Research Business Operations Street1*: 575 Lexington Avenue Street2: City*: New York County: New York State*: NY: New York Province: Country*: USA: UNITED STATES ZIP / Postal Code*: 10022-0000 Phone Number*: +1 646 962 4037 Fax Number: Email: grantsandcontracts@med.cornell.edu</p>				
6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)* 13-1623978				
7. TYPE OF APPLICANT* O: Private Institution of Higher Education				
Other (Specify): Small Business Organization Type <input type="radio"/> Women Owned <input type="radio"/> Socially and Economically Disadvantaged				
8. TYPE OF APPLICATION* <input checked="" type="radio"/> New <input type="radio"/> Resubmission <input type="radio"/> Renewal <input type="radio"/> Continuation <input type="radio"/> Revision		If Revision, mark appropriate box(es). <input type="radio"/> A. Increase Award <input type="radio"/> B. Decrease Award <input type="radio"/> C. Increase Duration <input type="radio"/> D. Decrease Duration <input type="radio"/> E. Other (specify):		
Is this application being submitted to other agencies?*		<input type="radio"/> Yes	<input checked="" type="radio"/> No	What other Agencies?
9. NAME OF FEDERAL AGENCY* National Institutes of Health		10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER TITLE:		
11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT* Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)				
12. PROPOSED PROJECT Start Date* 07/01/2024		13. CONGRESSIONAL DISTRICTS OF APPLICANT Ending Date* 06/30/2029 NY-012		

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE**14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

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 Province:
 Country*: USA: UNITED STATES
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15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	\$14,640,532.00
b. Total Non-Federal Funds*	\$0.00
c. Total Federal & Non-Federal Funds*	\$14,640,532.00
d. Estimated Program Income*	\$0.00

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

- a. YES THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
 DATE:
- b. NO PROGRAM IS NOT COVERED BY E.O. 12372; OR
 PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

I agree*

* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION

File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Aleta Middle Name: R. Last Name*: Gunsul Suffix:
 Position>Title: Exec Dir, Research Business Operations
 Organization Name*: Joan and Sanford I Weill Medical College
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 City*: New York
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 State*: NY: New York
 Province:
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 ZIP / Postal Code*: 10022-0000
 Phone Number*: +1 646 962 4037 Fax Number: Email*: grantsandcontracts@med.cornell.edu

Signature of Authorized Representative*

Aleta R. Gunsul

Date Signed*

11/20/2023

20. PRE-APPLICATION File Name:**21. COVER LETTER ATTACHMENT** File Name:

424 R&R and PHS-398 Specific

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Project/Performance Site Location(s)

Project/Performance Site Primary Location

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Joan and Sanford I Weill Medical College
UEI: YNT8TCJH8FQ8
Street1*: Weill Cornell Medical College
Street2: 1300 York Avenue
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10065-4805
Project/Performance Site Congressional District*: NY-012

Project/Performance Site Location 1

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

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UEI: LL8GLEVH6MG3
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Street2:
City*: Salt Lake City
County:
State*: UT: Utah
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 84112-8930
Project/Performance Site Congressional District*: UT-002

Project/Performance Site Location 2

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Ann & Robert H Lurie Childrens Hospital of Chicago
UEI: XJ7MMPHBMG7
Street1*: 223 E Chicago Avenue
Street2: Box 205
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County:
State*: IL: Illinois
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 60611-2605
Project/Performance Site Congressional District*: IL-007

Project/Performance Site Location 3

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Johns Hopkins University
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City*: Baltimore
County:
State*: MD: Maryland
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 21205-2196
Project/Performance Site Congressional District*: MD-007

Project/Performance Site Location 4

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Children's Research Institute
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Street2:
City*: Washington
County:
State*: DC: District of Columbia
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 20010-2916
Project/Performance Site Congressional District*: DC-098

Additional Location(s)

File Name:

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* Yes No

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? Yes NoIf YES, check appropriate exemption number: 1 2 3 4 5 6 7 8If NO, is the IRB review Pending? Yes No

IRB Approval Date:

Human Subject Assurance Number 00000093

2. Are Vertebrate Animals Used?* Yes No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? Yes No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* Yes No**4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*** Yes No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an Yes No environmental assessment (EA) or environmental impact statement (EIS) been performed?

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* Yes No

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* Yes No

6.a. If yes, identify countries:

6.b. Optional Explanation:

Filename

7. Project Summary/Abstract* Abstract.pdf**8. Project Narrative*** Narrative.pdf**9. Bibliography & References Cited** References Cited.pdf**10. Facilities & Other Resources** Facilities.pdf**11. Equipment** Equipment.pdf**12. Other Attachments**
Clinical Research Capabilities.pdf
DCC Capabilities.pdf
Available Populations.pdf
HEAL Public Access and Data Sharing Policy.pdf
Biospecimen Plan.pdf
Plan for Enhancing Diverse Perspectives (PEDP).pdf

PROJECT SUMMARY/ABSTRACT

More than 24,000 children develop acute respiratory failure (ARF) and require invasive mechanical ventilation (MV) – an intrusive, painful, yet lifesaving procedure – in the US each year. There is a critical knowledge gap regarding the optimal approach for analgosedation (analgesia-based sedation) in these children. As a result, the current standard-of-care is to provide opioids for the duration of MV. Despite high-dose opioid exposure, more than 90% of these children have suboptimal pain control. Studies show that repeated episodes of acute pain and prolonged opioid exposure put children at risk for chronic pain, opioid tolerance, withdrawal, delirium, and other negative effects. Yet, few randomized controlled trials (RCTs) target optimizing acute pain management in this high-risk population. In our study, ***Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)***, the central hypothesis is that a protocolized strategy of administering non-opioid adjuvant therapies to children with ARF will reduce pain and decrease opioid exposure. The primary objective of OPTICOM is to define the effectiveness of supplementing opioids with acetaminophen and/or ketorolac at decreasing episodes of acute pain in children with ARF on MV. This large-scale multi-site double-blind placebo controlled RCT will enroll 644 children across 14 pediatric intensive care units (PICUs) and randomize to one of 4 arms: Acetaminophen + Placebo; Ketorolac + Placebo; Acetaminophen + Ketorolac; or Placebo + Placebo. We will systematically monitor all children for acute pain for the first 5 days of IMV and quantify total opioid exposure in morphine milligram equivalents per kg as defined by the HEAL common data elements. Effects of acetaminophen and ketorolac will be determined using a 2x2 factorial design. This innovative proposal will leverage the extensive resources and experience of the Collaborative Pediatric Critical Care Research Network (CPCCRN) at executing clinical trials in the complicated PICU environment to achieve results within the 5-year study period. CPCCRN will ensure enrollment of a geographically, racially, and socioeconomically diverse patient population to allow for wide generalizability of study findings. By expanding HEAL-KIDS research into a unique and unstudied population, this project will lead to a paradigm shift in the care provided to critically ill children. Consistent with the goals of the Acute Pain Clinical Trials Program, the OPTICOM study will advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance our ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with ARF.

PROJECT NARRATIVE

Children with acute respiratory failure (ARF) require invasive mechanical ventilation (MV) – an intrusive, painful, lifesaving procedure. They universally receive high-dose opioids, yet still experience episodes of acute pain. ***Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)*** is a well-designed large-scale randomized controlled trial that will define the effectiveness of supplementing opioids with acetaminophen and/or ketorolac at (i) reducing pain and (ii) decreasing opioid exposure in this vulnerable population.

FACILITIES AND OTHER RESOURCES

The proposed project titled “**Optimizing Pain Treatment in Children on Mechanical Ventilation (OPTICOM)**” utilizes the resources of **Chani Traube (MPI)** and **Joy Howell** of Weill Cornell Medicine, **Michael Bell (MPI)** and **Vanessa Madrigal** of Children’s National Medical Center, **Richard Holubkov (MPI)** and **Ron Reeder** of the University of Utah, **Sapna Kudchadkar** of John Hopkin University, and **Erin Paquette** of Ann & Robert H. Lurie Children’s Hospital of Chicago. For the proposed studies, their resources are described below. **Biohazard protections relevant to the project activities can be found at the end of this section.**

WEILL CORNELL MEDICINE

Facilities of Dr. Chani Traube (Multi-PI - contact) and Dr. Joy Howell (Co-investigator)

Scientific Environment:

Weill Cornell Medicine (WCM) is committed to excellence in research, education, patient care, and the advancement of the art and science of medicine. The mission of the College is to provide the finest education possible for medical students and students pursuing advanced degrees in the biomedical sciences, to provide superior continuing education for the lifelong education of physicians throughout their careers, to conduct research at the cutting edge of knowledge, to improve the health care of the nation and the world, both now and for future generations, and to provide the highest quality of clinical care. The College is committed to the provision of health education, prevention, detection and treatment of disease, and the development of a research agenda and public health policy responsive and sensitive to the needs of the community. Weill Cornell Medical College is dedicated to the tripartite mission of education, research, and patient care.

Founded in 1898 and affiliated since 1927 with what is now New York-Presbyterian Hospital, Weill Cornell Medicine is the #14 ranked medical college in the country for research (US News and World Report, 2023). **New York-Presbyterian Hospital is the #7 ranked hospital** in the country (US News and World Report, 2023). Weill Cornell Medicine and Weill Graduate School of Medical Sciences are accredited by the Liaison Committee for Medical Education of the American Medical Association and the Association of American Medical Colleges.

Weill Cornell Medicine is one of 14 college/school units comprising Cornell University. The Medical College provides training and education to 439 medical students, 883 graduate students and 475 post-doctoral fellows. Currently, 1,700 full-time faculty members work throughout 8 basic science and 22 clinical departments. The basic science and clinical departments are located in multiple, tightly clustered buildings straddling York Avenue between 68th and 72nd Streets on Manhattan’s Upper East Side. Several off-site buildings house administrative and clinical offices.

WCM has increased its annual operating budget to more than \$2.2 billion and quadrupled clinical revenue in the past decade. Total annual research support exceeds \$340 million which represents federal government, non-federal sponsored research grants, training grants, and fellowships. WCM is one of the fastest growing medical schools in clinical revenues and research funding (AAMC, 2019) and possess one of the highest percentage of medical student graduates who are currently in academic medicine nationally (AAMC, 2019). The extraordinary growth in extramural research funding led to the opening of a state-of-the-art research building focused on translational and basic research, the Belfer Research Building, which houses a \$650 million, 16-story, 480,000 sq. ft. state-of-the-art research hub. This building is devoted to translational and basic research areas in cancer, cardiovascular disease, lung diseases, metabolic diseases, neurodegenerative diseases, children’s health, global health, and infectious diseases.

The academic environment within the Weill Medical College of Cornell University combines the high clinical volume of its tertiary health care facility with focused basic science research. In particular, the Medical College has since raised funds to begin construction of a translational research facility across the street from the Hospital within the next year. The tri-institutional setting of Cornell, Memorial Sloan Kettering Cancer Center, and The Rockefeller University has further created an environment open to scientific collaborations and spirited debate. The three institutions are located within one block from one another (5-minute walk) and have historically integrated their research efforts.

As part of the multidisciplinary, collaborative approach undertaken at the Weill Medical College of Cornell University, several research conferences have been established to promote career development plans and research efforts, particularly among the young faculty. The academic environment at Cornell is augmented by

several other weekly conferences including Urology Grand Rounds, The Tri-Institutional Immunology Research Seminar Series sponsored by Weill Cornell, the Hospital for Special Surgery, and the Sloan Kettering Institute; the Weill Graduate School Immunology Program Research in Progress Series; and the Division of Immunology (Medicine) Research Meetings.

The Clinical and Translational Science Center (CTSC) addresses the necessity of an integrated, comprehensive research support system that includes education, training and mentoring for clinical research investigators, coordinators and staff. The mission of the CTSC is to provide an environment that allows optimal use of our considerable multi-institutional assets and the diversity of our patient population to move translational research seamlessly from bench to bedside and to the community. The CTSC partner institutions include: WCM, Weill Cornell Graduate School of Medical Sciences, Cornell University-Ithaca, Cornell University Cooperative Extension, Memorial Sloan Kettering Cancer Center, Hospital for Special Surgery, Hunter College School of Nursing, Hunter College School of Urban Public Health and the Animal Medical Center. The CTSC includes federally and privately sponsored multi-center trials, training grants, and individual awards as seed grants to investigators. It provides opportunities for qualified investigators to advance medical knowledge from the laboratory bench to the clinical bedside. It also has a comprehensive clinical and translational training program designed to stimulate and enhance careers and training in clinical research for medical students and junior investigators. The CTSC acts as a conduit through which essential resources, technological tools and education programs for all partners can be efficiently shared and managed. Integral to Weill Cornell's Strategic Plan for Research, which was initiated seven years ago, the plan for the CTSC brought to fruition the integration of existing inter-institutional resources among neighbors on York Avenue and partner institutions in the immediate area. The resulting cluster of East Side institutions forms a unique and cohesive biomedical complex fulfilling the NIH roadmap initiative of breaking down institutional silos and barriers separating scientific disciplines to accelerate the clinical application of basic science discoveries. This center is funded through the Clinical and Translational Science Awards (CTSAs), a national consortium that is transforming how clinical and translational research is conducted.

The Department of Pediatrics at WCM has a long and distinguished tradition of leadership in pediatric care, education, and research. As of 2020 there are 14 subspecialty divisions within the department, dozens of associated programs, services, clinics and outpatient care sites. The Department remains a leading regional referral center. **The Department of Pediatrics is Drs. Traube's and Howell's academic home at WCM.** It is comprised of 13 divisions and has more than 152 full-time faculty members. In the Fiscal Year 2022 (07/01/2021-06/30/2022) the Department of Pediatrics supported and managed a total of 117 individual research grant awards, 42 individual funded investigators, with collective project total costs of 22.1M. In the same period the Department supported 290 IRB protocols for 97 individual principal investigators.

The Center for Research on End-of-Life Care (CREC): CREC's primary mission is to conduct research dedicated to the discovery of mechanisms and the testing of interventions to improve the quality of life of not only patients, but also their family caregivers. As part of its mission, CREC also aims to reduce inequalities in the delivery of health care. Since CREC's founding in January 2014, it has been awarded numerous research grants summing to over \$20 million dollars. These funds have fostered the development of a thriving research environment of multidisciplinary faculty, social workers, nurse interventionists, research coordinators, statisticians, grants and database managers, as well as administrative and regulatory staff. CREC has now expanded its work to include parents of critically ill children who are expected to survive the PICU stay.

Clinical Environment:

New York Presbyterian Hospital (NYPH) is the nation's largest not-for-profit, non-sectarian hospital, with 2400 beds, 2 million patient visits per year, 6144 affiliated physicians, and five major centers in New York. NYPH is unique in its affiliation with two leading Ivy League medical schools: WCM and Columbia University. NYPH is one of the top ranked hospitals in the country and on the honor roll. NYPH patients come from varied ethnic, cultural, and socioeconomic backgrounds, reflecting the wide referral pool for this institution. Patients are referred locally, from institutions throughout New York state, the United States, and the world. This breadth of backgrounds provides a diverse population for inclusion of many ethnic groups in ongoing clinical research.

The Phyllis and David Komansky Center for Children's Health is a multidisciplinary children's hospital within a hospital among the nation's leading centers for pediatric care, medical education, and children's health research. Together with our affiliate Weill Cornell Medicine, NYP Komansky Children's Hospital is committed to

improving the health and wellness of infants, children, and adolescents through high-quality and comprehensive programs guided by family-centered patient care. Moreover, we are striving to eliminate healthcare disparities through improving access and advocacy for health equity. In addition to world-class clinical programs, Komansky Children's Hospital is a leader and innovator in medical education with a robust and competitive residency program, fellowships across the specialties, and a new Physician Scientist Training Program (PSTP). Our doctors, residents and fellows are among leading pediatrician scientists seeking new therapies and cures through basic and clinical research.

The Pediatric Intensive Care Unit (PICU) is a multidisciplinary environment providing state-of-the-art care to children with life-threatening medical and surgical conditions. The division has 11 faculty members and 7 fellows. The PICU consists of 23 beds, and admits approximately 1400 patients per year. It is equipped and staffed to care for critically ill infants, children and adolescents around the clock. The PICU is racially and ethnically diverse and has a high volume of patients to support recruitment into the study, as well as family meeting rooms and experience with telehealth/videoconferencing for web-based access to the intervention. Dr. Traube is a senior attending physician in the PICU, and led recruitment for the pilot study of EMPOWER in PICU parents. Thus, the clinical environment is proven, very supportive, and fertile – in a word, outstanding -- for the proposed study.

Computer: Drs. Traube, Howell, and staff have access to secure, networked desktop, laptop, and tablet computers that will enable direct data entry into the centralized REDCap project database. The Office Information Technologies and Services (ITS) provides comprehensive computer support, networking, e-mail, web design, server management, and database development for Cornell University and Weill Cornell Medical College. ITS supports ~ 4,000 computer users, 58 servers and numerous advanced database systems. It has created thousands of high-traffic web pages, several major database-driven sites and research data repositories. In June 2017, the Weill Research Gateway (WRG), an online portal for research administrative tools, was launched for use by faculty and staff at the institution. WRG has streamlined our pre-award/ contract processes by enabling system-to-system grant submission for several federal agencies and proposal/contract routing, as well as serving as a repository for grant and contract documentation.

Office: Dr. Traube's office is located in the M building of the WCM/NYPH, and Dr. Howells's office is located in the nearby CREC suite at Lasdon house. Both have private offices, needed electronics and internet access and networking capabilities, conference rooms, and administrative support.

ADDITIONAL INSTITUTIONAL RESOURCES:

Office of Research Administration: This office has been established in the Department of Pediatrics in September 2018. Drs. Katherine Hajjar, MD and Sujit Sheth, MD serve as co-Directors for this group. The team includes an experienced research administrator in a role of the Administrative Director, Grant Specialist, and Accounting Specialist. Collectively, this team facilitates basic and clinical research functions in the Department including identification of suitable funding opportunities, application development, financial management of research funding, progress and final report submissions, and applicable regulatory compliance. Additional Support is provided by the **Research Business Operations (RBO)**, as described below. **Program Management** resources are available through the Department of Pediatrics. Clinical research support resources are available in individual Divisions and centrally through the collaboration with the **Joint Clinical Trials Office**.

Program Management Team (PMT): The Department of Pediatrics has a team dedicated to supporting the programmatic needs investigators in the Department of Pediatrics to ensure a smooth transition and efficient execution of regulatory and programmatic requirements as well as administrative staff for coordination of required meetings. The PMT has experience in efficiently executing multiple P01 Program Projects and U01 Clinical Studies (with multi-sites) with budgets of >\$15M per year. They work seamlessly with the Research Business Operations Office and central Office of Sponsored Research Administration (OSRA) to ensure appropriate allocations and contract executions are complete.

Research Business Operations (RBO): RBO offers targeted, end-to-end, research portfolio management for WCM Centers, Institutes, and research investigators. These include the following:

- Grant proposal preparation - Including proposal building and editing, budget development, JIT preparation, and grant transfer management.
- Contract Processing – Including routing contract documents for Central Administration review (e.g. Clinical

Trial Agreements, Sponsored Research Agreements, BioPharma Alliance Agreements, Material Transfer Agreements, Data Use Agreements and Non-Disclosure Agreements)

- Award & Fund Management – Including grant and fund set-up verification, financial monitoring of sponsored research, review and approval of expenditures, progress report management, subcontract document preparation, etc.

Office of Sponsored Research Administration (OSRA): OSRA supports the WCM research community by helping WCM faculty find and pursue viable research opportunities and manage their awards from inception to closeout. OSRA serves as the liaison between Principal Investigator(s) (PIs) and Sponsors so researchers can focus their time and talent on science. The team liaises closely with Grant Accounting, JCTO, University Counsel, CTL, IRB, IACUC, EHS, Conflicts Management Office and Research Compliance departments. In addition to shaping institutional policy to promote and protect faculty research and creativity OSRA is responsible for the following activities: Facilitate pre-award activities on behalf of Principal Investigators, authority to review, approve, and submit grant and contract proposals on behalf of WCM, review and submit actions requiring sponsor prior approval.

Joint Clinical Trials Office (JCTO): The Department of Pediatrics (DoP) maintains an active collaboration with the Joint Clinical Trials Office (JCTO) that provides regulatory and data management for clinical studies. The JCTO has been established at WCM and NYP in 2013 to foster and advance clinical research programs. Today this central administrative team performs multiple functions at the institution, including the Clinical Trials Operations Unit that focuses on investigator support and training, study design and feasibility, and facilitating access to resources that streamline the conduct of clinical trials. The Department of Pediatrics employs:

- Three Clinical Research Supervisors with expertise in regulatory, data management, and team management
- One full-time Regulatory Specialist
- Four full-time Research Specialists
- Five full-time Clinical Research Coordinators.

The DoP team is headed by an experienced Clinical Trials Administrator, and it is supervised by the Associate Director of the JCTO. Collectively, this unit is responsible for support and management of the majority of clinical research studies at the Department. This allows us to maintain unity, standards and the highest quality of data and regulatory management for clinical research.

Institutional Commitment to the Early-Stage Investigators (ESIs): The mission of the Weill Cornell Medicine Office of Faculty Development (OFD) is to build and sustain faculty vitality through the recruitment, retention, and advancement of a diverse faculty community. Mentoring is a major strategic priority and essential to the growth and success of faculty. Within the OFD, the Faculty Advancement & Research Mentorship Program (**FARM**) for Junior Faculty is designed to mentor junior faculty without an R01 or equivalent through grant submission process. FARM's NIH funding success rate is 65% for junior investigators compared with 19% national average. Each FARM cycle starts with this two-day workshop that covers topics on grantsmanship. It continues with longitudinal support provided by a committee of faculty mentors with biweekly meetings where individual proposals are reviewed.

Department of Pediatrics Faculty Mentoring Program (FMP)

The Department of Pediatrics is invested in and deeply supportive of academic growth and the success of all its faculty members. To that effect, we implemented a Departmental Faculty Mentorship program to support the professional development of our junior faculty. The goal of this program is to provide individualized support to help junior faculty identify a mentoring team and tailored plans to achieve success and career fulfillment.

The mentoring program supports academic employees at the following appointment levels:

- Postdoctoral Associate/non-ACGME Fellow (required for the duration of the appointment)
- Instructor (required for the duration of the appointment)
- Assistant Professor (required for the first three years of the appointment)
- Associate Professor (voluntary participation)

Junior Faculty (program tracks 1-4): Depending on the program track, faculty members develop and implement their career and research plans. The program provides organized guidance from mentoring teams composed of faculty members at WCMC and collaborating institutions.

Trainees (program track 5): This track was created specifically for Postdoctoral Associates. The program offers two one-on-one meetings per year for the trainee to discuss their individual goals and needs with the Program Lead (Dr. Genevieve Fouda, The Assistant Dean for Faculty Development at WCMC) and the program administrative team. In addition, there is one annual full mentoring committee meeting that brings together all mentors, including the primary mentor and any other person identified for the group. The program offers monthly Professional Development series on an expansive range of topics. These presentations are recorded and made available to all participants of the FMP. Included with these meetings are conversations with junior faculty at WCMC who share their experience and knowledge on the transition from PostDoc to faculty roles. Also included with this program is the annual PostDoc Day, an in-person event that showcases presentations from all program trainees and from key institutional faculty and leadership.

Mid-level Faculty (program track 6): Mid-level faculty join the mentoring program on a voluntary basis. This track focuses on providing overall guidance and peer mentoring. To that effect. The program offers peer-mentoring sessions and one-on-one advice as needed.

WEILL CORNELL COLLABORATION AND DATA MANAGEMENT RESOURCES

Secure Data Sharing through Box or SharePoint: The study team will utilize a secure web-based study folder created through Box or Microsoft Sharepoint to upload and share study-related documents and data. No personal identifiers will be included in shared documents or data. Box protects data using encryption and access controls and all communication with Box from a computer and/or mobile device is encrypted using SSL. Data is encrypted in storage using 256-bit AES encryption. Only key personnel on the study from each site will be granted access to this folder on Box under the management of the Research Program Manager.

Data Management using Research Electronic Data Capture (REDCap). The Clinical & Translational Center (CTSC) provides research support services to Principal Investigators and Study Coordinators. A key service for the proposed project is access to Research Electronic Data Capture (**REDCap**), a mature, secure web application for building and managing online databases with data validation which provides automated export procedures for seamless data downloads to Excel and common statistical packages (SPSS, SAS, Stata, R). REDCap (J Biomed Inform. 2009 Apr;42(2):377-81; PMCID: PMC2700030) will be used as the data repository for internal sharing of Program-generated data.

WCM uses REDCap for management of clinical research data and other research data, and it is also used by more than 300 universities participating in the NIH Clinical and Translational Science Award (CTSA) consortium. REDCap does not require client local software and can be accessed from anywhere on the Internet via a secured server. REDCap provides: 1) a stream-lined process for rapidly building a database; 2) an intuitive interface for collecting data (with data validation) and audit trails; 3) automated export procedures for seamless data downloads to common statistical packages (SAS, SPSS, etc.); 4) branching logic, file uploading, and calculated fields; and 5) a quick and easy protocol set-up. Use of REDCap ensures data provenance and security.

WCM Institutional Data Repository for Research (WIDRR). The WCM Institutional Data Repository for Research (WIDRR) is a tool designed to help researchers comply with the new Cornell University Data Management and Sharing Policy. This policy requires all WCM researchers to create a data retention record in WIDRR that indicates the location of each research dataset created with federal funds, along with a document detailing the different steps used to analyze the raw data up to the stage where the data are publication ready. Data from Lab archives, Box, OneDrive can all be integrated and shared with external collaborations for efficient and dedicated data exchange.

NVivo: NVivo is a software program used for qualitative and mixed-methods research. Specifically, it is used for the analysis of unstructured text, audio, video, and image data, including (but not limited to) interviews, focus groups, surveys, social media, and journal articles. It is produced by QSR International.

CHILDREN'S NATIONAL HOSPITAL AND CHILDREN'S NATIONAL RESEARCH INSTITUTE (CNH, CNRI) Facilities of Dr. Michael Bell (Multi-PI) and Dr. Vanessa Madrigal (Co-Investigator)

CTSI-CN at Children's National Hospital (CNH)- INVENTA TOWERS

In November 2019, CNH signed a 15-year lease agreement for four floors comprising 140,000 square feet of office and clinical space at the former Discovery Health building in downtown Silver Spring, MD. This building,

called Inventa Towers, is 5 miles from the main CNH campus, 1.5 miles from the new Children's National Research & Innovation Campus, and 7 miles from the main GW campus.

CTSI-CN now occupies 17,950 sq. ft. on the 4th floor of this newly remodeled building. This 9,340 sq. ft. office suite includes several conference rooms, state-of-the-art audiovisual facilities, and technology that allows a "hands-on" remote approach to communication and teaching, numerous administrative and faculty offices, and workstations as well as IT and storage capacity. This suite will house the CTSI-CN leadership offices (Dr. Guay-Woodford) as well as administrative functions of BERD, Informatics, CaMR-AN, and the Data Science Accelerator. In this new home, CTSI-CN shares a floor with the CNH Center for Translational Research, and is in close proximity with CN Offices of Grants and Contracts Administration, Human Subjects Protections, Legal Risk and Compliance on the 3rd & 5th floors of the building.

On the 7th floor of the Inventa building is a 3,700 sq. ft. outpatient clinical facility to support CRC research protocol encounters. Specific accommodations of the CRC include: exam and consult rooms for non-infusion and non-PK visits with study patients; laboratory support for sample processing, storage and shipment, and DNA/RNA extraction services. The CRC will maintain a small footprint at the Shaikh Zayed main CNH campus to conduct research infusions and lab processing of scatter visit specimens.

The Inventa building will also house the Fight for Children Sports Medicine Center, a philanthropically supported program which will provide rehabilitation services, performance enhancement and injury prevention education and community outreach, and research. It will also offer consultations and treatment through CNH's growing footprint of outpatient clinics around the city, paired with partnerships with DC schools.

McGehee Joyce Clinical Research Center (CRC)

Children's National Research & Innovation Campus at Walter Reed: The new Children's National Research & Innovation Campus (RIC), a first-of-its-kind pediatric research and innovation hub, is located on a nearly 12-acre portion of the former Walter Reed Army Medical Center. The RIC is situated 5 miles from the main GW campus, 1.5 miles from Inventa Towers, and 4.3 miles from the main CNH campus. The RIC will initially focus on high-impact research in pediatric genomic and precision medicine anchored by the Center for Genetic Medicine Research and the Rare Disease Institute, which welcomed its first occupants in February 2021. Other occupants, including the Center for Genetic Medicine Research, will begin to move on July 1, 2021.

With its proximity to federal research institutions and agencies, universities, and academic research centers, the RIC will be able to leverage public and private sectors to help advance innovation. Further bolstering this innovative environment, Johnson & Johnson, LLC and CNH's collaboration to launch JLabs @ Washington, DC, a life science incubator that will house up to 50 start-up companies from across the pharmaceutical, medical device, consumer and health technology sectors. Johnson & Johnson and CNH have a long-standing history of innovating for children, including as co-founders of Safe Kids Worldwide, a nonprofit organization aiming to help families and communities keep kids safe from injuries. JLabs @ Washington, DC includes 32,000 square feet of lab and office space and will be located within the RIC. With the opening of JLabs @ Washington, DC, Johnson & Johnson Innovation aims to strengthen and expand the region's network to attract the full breadth of science and technology innovators who are focused on developing transformative solutions to improve patients' and consumers' lives, while also complementing the Children's National mission – to drive discoveries that are then rapidly translated into new treatments and technologies benefitting children, adolescents and adults. JLabs @ Washington, DC is the hub for BLUE KNIGHT™, a collaboration with the Biomedical Advanced Research and Development Authority (BARDA), a component of the U.S. Department of Health and Human Services. Blue Knight aims to stimulate innovation and incubation of science and technologies that improve health security response. From inception, the RIC has been designed to nurture innovation from discovery to commercialization of therapeutics, diagnostics, and devices that will advance the health and well-being of babies and children around the world.

Children's National Research Institute (CNRI): is the research and training arm of CNH, with more than 450 scientists, trainees, and staff members. CNRI occupies 100,000 sq. ft. of laboratory space on the 5th and 6th floors of the main hospital. The annual CNRI NIH grant portfolio has grown from \$6 million in 1998 to more than \$48 million in 2020; the total grant portfolio increased from \$12 million to \$75 million during this period. Research at CNH has become a focal point for multi-institutional projects in the DC area and nationally. CNH has provided over \$85 million in intramural programmatic support for research activities since FY2016. In addition to this funding, CNH has recruited a development officer to work on behalf of CNRI, and additional funds raised through philanthropy are added to the endowment base.

Research at CNH is highly collaborative and multi-disciplinary. Nearly all laboratories and clinical divisions work together to answer questions about childhood diseases. The research space is located at the CNH Sheikh Zayed Campus for Advanced Children's Medicine building, which creates an environment where scientists and physicians can more easily collaborate on innovative projects that will improve patient care.

CNRI is organized into five programmatic centers:

Center for Translational Research: In 2012, the Center for Translational Research was organized around three pillars of investigator-initiated research: 1) Molecular Pathogenesis and Experimental Therapeutics; 2) Patient Oriented Research; and 3) Behavioral and Community Research. Research in these areas spans the full translational continuum. The main footprint of the Center occupies 10,000 sq. ft of office space and conference rooms on the 4th floor of the Inventra building, where it moved from the main CNH campus in late 2020.

Based on a center-wide strategic planning process in 2019, the Center expanded its focus to a broader framework based on EL Boyer's principles of academic scholarship. This model, which includes: 1) the scholarship of discovery (hypothesis-driven research), 2) the scholarship of team science, 3) the scholarship of clinical care, and 4) the scholarship of education, more accurately encompasses the scholarly activities of the Center's >110 members. The Center research activities are enhanced by the close partnership with CTSI-CN and are supported by extramural funding from NIH, other federal agencies, foundations, and industry.

Center for Genetic Medicine Research (CGMR): was established in 1999 with the goal of an open, collaborative, multi-disciplinary network of genetic medicine researchers. The Center has a highly interdisciplinary faculty focused on defining the genetic basis of common health problems in Washington, DC, as well as serving as an international referral site for rare disorders. The Center receives funding from the NIH and other federal, foundation, and philanthropic sources. A total of 38 investigators have CGMR appointments. The emphasis of CGMR is on translational research and emerging technologies (genomics, proteomics, large-scale public access databases). It currently comprises approximately 18,000 sq. ft. in an open laboratory infrastructure and houses an independent computing infrastructure and support personnel, and extensive equipment for high-throughput data generation at the CNH main campus. CGMR will be moving to the RIC in August 2021, part of Phase 1 of the RIC transition.

The infrastructure is extensively utilized by investigators from CNRI, the greater metropolitan DC area, and internationally through a series of funded Core programs. CGMR has more than \$8 million of state-of-the-art equipment available for support of all types of genomics, proteomics, microscopy, bioinformatics, pre-clinical (mouse) drug trials, and multi-site clinical trial networks.

Center for Cancer and Immunology Research (CCIR): has a total of 15,000 sq. ft. of wet laboratory space at CNH main campus. The Center currently has 11 research faculty and 20 affiliated clinical faculty. Among the research faculty are 8 cancer biologists and 5 immunologists. With interests spanning T cell biology, inflammation, cancer immunology, transplantation, and autoimmune diseases, CCIR immunologists often contribute to CTR research at the hub.

Over the past 2-3 years, CCIR has made major contributions in advancing the understanding of key signaling pathways involved with brain tumor development, implementing several key first-in-human studies utilizing novel cell therapies for the treatment of cancer as well as life-threatening viral infections. In 2019, CCIR was awarded a \$1.5 million gift from the Children's National Board of Visitors to support immunotherapy research at CNH. In addition, under a memorandum of understanding with GW, immune cell therapy research has been expanded to GW as a joint CNH-GW program. CCIR will be moving to the RIC as part of Phase 2 of the RIC transition, with a target date of 2025.

Center for Neuroscience Research (CNR): The Center's goal is to understand the development of the central nervous system and the cellular and molecular mechanisms of brain dysfunction in order to prevent or treat neurological and behavioral disorders of childhood. The Center comprises a group of 35 highly productive lab-based developmental neuroscientists and clinical investigators who have established strong research programs and collaborations in neurodevelopmental disorders.

CNR's unique and exciting setting has supported and promoted research projects that span basic, translational, and clinical research in neurodevelopmental disorders, with eight major areas of focus including: neural stem cells and developmental neurobiology, brain injury and brain protection, perinatal hypoxia and hyperoxia, epilepsy, neuro-oncology, neurofibromatosis, attention deficit hyperactivity disorder, and autism. The Center occupies approximately 12,000 sq. ft. of open lab space and support rooms for infrastructure/cores (e.g. cellular imaging, electrophysiology, neural stem cells, and gene gain- and loss-of-function) at CNH main campus. The

NIH-funded Intellectual and Developmental Disabilities Research Center (IDDRC) Neuroimaging Core is housed in this Center. CNR will be moving to the RIC as part of Phase 2 of the RIC transition, with a target date of 2025

Sheikh Zayed Center for Pediatric Surgical Innovation: Launched in September 2009, the Sheikh Zayed Institute for Pediatric Surgical Innovation (S2I) at Children's National is redefining what is possible in surgery through innovative, integrated research. S2I's physician-scientists are applying their expertise in their specialized fields to pursue the common goal of making pediatric surgery more precise, less invasive, and pain-free. By combining research and clinical work in this area, S2I is developing knowledge, tools, and procedures that will benefit children in the DC area, across the country, and around the world.

Situated at the main CNH hospital, the S2I has 22,000 sq. ft. of laboratory and office space that facilitates current and future research collaborations with its glass walls and white board-lined corridors. Clinicians work side-by-side with scientists and bioengineers, identifying challenges and exploring solutions, while trainees and students present their work every week alongside faculty during Innovation Rounds.

Pediatric Pharmacology Research Unit (PPRU): supports investigators in the design and conduct of pharmacological studies of both new and off-patent drugs in neonates, infants, and children. These investigations aim to improve the labeling of drugs for use in pediatric patients. The PPRU enables the research necessary to elucidate the impact of pharmacogenetics/pharmacogenomics and growth and development on drug disposition and action in neonates, infants, children, and adolescents. Incorporating this new knowledge in pediatric pharmacotherapy and in the design of new studies will lead to more safe and efficacious drugs for all children. As part of a National PPRU Network, the PPRU at CNRI further facilitates collaboration with other academic institutions as well as the FDA, NIH, and pharmaceutical industry. It has been very helpful in setting up paradigms for the Urea Cycle Disorders Consortium (UCDC) clinical trials, part of the NCATS-funded RDCRN network.

Clinical Environment:

The McGehee Joyce Clinical Research Center (CRC) occupies 5,800 sq. ft. on the 3rd floor of the main hospital in the same building as the Innovation and Learning Center and related CTSI-CN laboratories. The CRC has six outpatient beds, two infusion chairs, and one exam room. It offers support in: 1) Clinical Research Nursing and in-hospital services (drug infusions, PK testing, physical exams, vitals, blood collection, sample processing and shipping, medication administration; 2) Laboratory Support (sample processing, storage and shipment, DNA/RNA extraction services); 3) Study Coordination and Regulatory Submissions Support (study coordination, pre-award and post-award support); 4) Research Pharmacy (drug administration and drug infusion support in coordination with Investigational Drug Services); and 5) Cardiovascular Testing (ECG, telemetry, ambulatory BP, pulse oxymetry).

Children's National Hospital (CNH) is the only exclusive provider of pediatric care in the metropolitan Washington, D.C. area and is the only freestanding children's hospital between Philadelphia, Pittsburgh, Norfolk, and Atlanta. Serving the nation's children for 150 years, the internationally recognized pediatric healthcare professionals at CNH care for more than 360,000 patients each year who come from throughout the region, nation, and world. There are approximately 16,000 inpatient admissions, 683,855 outpatient visits and over 120,000 emergency department visits annually. Serving as an advocate for all children, CNH is the largest non-governmental provider of pediatric care in the District of Columbia, providing more than \$50 million in uncompensated care. CNH is a proven leader in the development and application of innovative new treatments for childhood illness and injury. In 2020, the US News and World Report ranked Children's National the 7th best pediatric hospital in America.

Children's National includes a 323-bed hospital, five community-based health centers in the District of Columbia, and seven regional outpatient facilities in Maryland and Virginia. In addition to over 700 full-time faculty members affiliated with the GW School of Medicine and Health Sciences, there are more than 600 community pediatricians affiliated with CNH through its Children's National Health Care Network, many of whom share a common electronic medical record with CNH.

Pediatric Health Network (PHN) was established as a CNH affiliate to transform the health of children in the greater DC metro area through coordinated and collaborative care among pediatric primary physicians, specialists, hospitals, and community partners. The PHN is comprised of 61 primary care practices with 523 primary care physicians in addition to >1,000 CNH specialty care physicians that provide care for >500,000 infants, children, and adolescents in the greater DC metro area.

CTSI-CN is the logical partner for the PHN in its mission to establish a learning community that "improves quality of care, including the promotion of best practices and evidence-based approaches to increase quality and reduce variability of care across the provider network". Our first collaborative initiative aims to capture real world data about functional abdominal pain (e.g. incidence, prevalence, contributing factors, diagnostic costs) and from

these data design a real-world intervention trial. This initial project will serve as a model for real world evidence research to assess contributing factors, streamline diagnostic testing, evaluate interventions, and reduce costs (see Section F. Hub Research Capacity).

Administrative Support: The faculty and staff supporting the Biostatistics, Epidemiology and Research Design (BERD) module of the CTSI-CN are housed in a 2,500 sq. ft. office suite at a CNH facility in Silver Spring, MD – approximately 5-miles from the main CNH campus. This office suite was completely renovated in 2016 and provides a state-of-the-art facility that includes conference rooms, video conferencing capabilities, and administrative and faculty offices. From this facility, the BERD maintains effective collaborations with the BERD faculty and staff at GW as well as investigators through governance meetings, conferences, distance education capabilities, and cores; this location provides the functional "home" and point of contact for the BERD.

Bear Institute Innovation and Learning Center: The CNH Bear Institute Innovation and Learning Center occupies approximately 4,950 sq. ft. on the 2nd floor of the main hospital. The center was a CTSI-CN administrative location until the move to Inventia in 2020, and it houses the CNH Department of Nursing Research as well as a Cerner Innovation Team. The Center serves as an organizing hub, bringing together clinical, research, and technical experts who will work to enhance many of the clinical, patient safety, quality, education, and research activities within the healthcare system and the research enterprise. CTSI-CN will have access to hoteling space in this center for instances in which administrative staff and faculty require on-site working space at CNH.

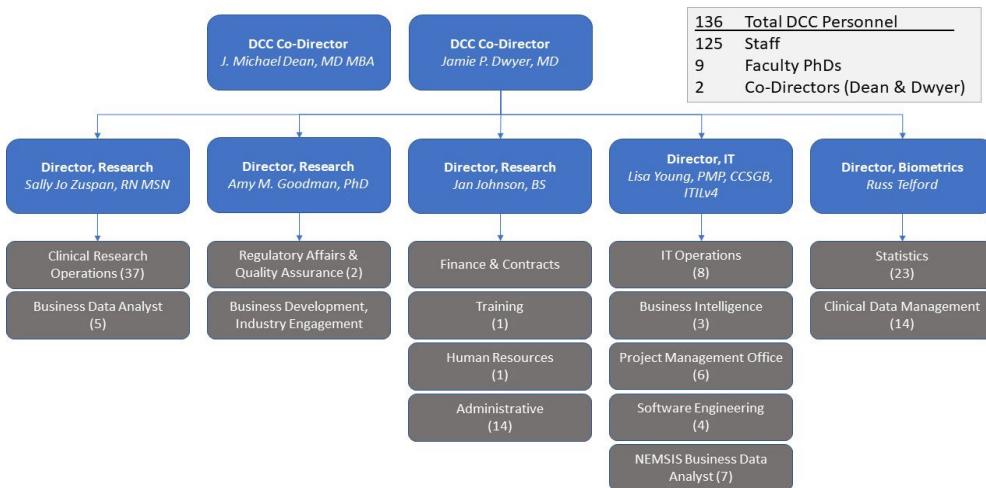
UNIVERSITY OF UTAH (DATA COORDINATING CENTER)
Facilities of Dr. Richard Holubkov (Multi-PI) and Dr. Ron Reeder (Co-investigator)

The University of Utah Data Coordinating Center (Utah DCC) was founded in 2001 and has provided data, statistical, and clinical coordinating center support for 12 national research networks (Table 1) and has implemented over 140 active or completed multi-center studies resulting in over 500 publications through June 2023.

Table 1: National research networks coordinated by the Utah DCC.

Network	Year Initiated
Pediatric Emergency Care Applied Research Network (PECARN)	2001
Collaborative Pediatric Critical Care Research Network (CPCCRN)	2005
Hydrocephalus Clinical Research Network (HCRN)	2006
The Network of Pediatric Multiple Sclerosis Centers	2010
Neuromyelitis Optica Research Network	2012
Adult Hydrocephalus Clinical Research Network (AHCRN)	2013
Fetal Heart Society (FHS)	2014
Pediatric Colorectal and Pelvic Learning Consortium (PCPLC)	2016
Four Corners Youth Concussion Research Network (4CYC)	2016
Trial Innovation Network	2016
Scleroderma Foundation Research Network	2018
Helping to End Addiction Long-term Effectiveness Research Network (HEAL ERN)	2019

Senior Leadership and Organization: The Utah DCC is a full-service academic research organization (ARO) that provides comprehensive research support from concept development through protocol implementation and manuscript production. The DCC has a 21-year history supporting investigators from across the country to develop and implement a wide range of research projects and providing research support and expertise to multiple national clinical research networks. Our mission is to *accelerate research to the bedside for the benefit of patients across the lifespan*. We fulfill this mission by providing clinical and biostatistical leadership at the faculty level, statistical analysis, data management, project management, regulatory expertise, and comprehensive Information Technology (IT) systems to support multi-center clinical research. Our leadership brings substantial clinical expertise in pediatric and adult medicine, and our location inside an academic medical center provides access to clinical and research experts in many other areas. Drs. Dwyer and Dean provide stable leadership and broad experience in clinical research and grant writing. Dr. Goodman, Ms. Zuspan and Ms. Johnson bring substantial clinical, operational, and clinical trial experience. Our leadership group is rounded out by experienced senior managers and directors (**Figure 1**).



Computing Resources-Hardware: The Utah DCC provides data coordination and management services for numerous national research networks and multi-center observational studies and interventional trials. Anchoring these services is a state-of-the-art, energy efficient data center. The data center facility supports more than 3500 users around the country and provides a secure, reliable, enterprise-wide infrastructure for delivering mission-critical DCC systems for its clients.

In addition to the on-premises data center, the DCC operates major workloads in the Amazon Web Services (AWS) cloud. DCC IT staff are experienced in architecting infrastructure to meet AWS's Well-Architected Framework. The IT staff are experienced in supporting cloud-native and lift-and-shift applications.

IT Services: The IT group is comprised of network infrastructure architects, system administrators, software design engineers, technical support analysts, business intelligence (BI) developers, data architects, and IT PM. The DCC offers end-to-end technical solutions to meet business needs, including the design and development of secure systems to receive, process, and store clinical research data.

Enterprise Infrastructure Architects design and implement the conceptual and logical information systems that support the enterprise infrastructure. The architect utilizes cross-functional knowledge in change management and business process management to ensure the underlying technical architecture and information systems meet the needs of the business.

Systems Administrators maintain the entire technology stack, which includes the upkeep, configuration, and reliable operation of all servers, databases, systems, and permissions to those resources.

Software Design Engineers work with product owners, PMs, program directors, and faculty to design and develop custom technical solutions, such as highly available web services, data transformation processes, websites, registry systems, and other innovative services.

Technical Support Analysts provide in-person and remote technical support for users of DCC systems, including granting and troubleshooting permissions to DCC resources.

Business Intelligence Developers are responsible for developing, deploying, and maintaining dashboards and reports to share valuable information with clinical research stakeholders. The BI team leverages technologies such as Tableau, SharePoint, and Power BI to display analytic data. Data Warehouse Architects are responsible for designing and actively maintaining data management solutions, such as databases, data warehouse, and

the movement of data (ETL - extract, transform, load) processes.

IT PMs oversee the planning and implementation of IT projects. IT PMs partner closely with software design engineers, systems administrators, and BI developers to design and deploy solutions that are in alignment with budget, scope, and schedule.

Facility, Hardware, Storage, Data Backup and System Availability

The data center was built using industry standards and energy efficient cooling solutions. The data center is cooled by Liquid Cooling Package (LCP) inline cooling technology, providing the desired efficiency, redundancy, and modularity. The LCP utilizes a hot- and cold-aisle design that allows for even air distribution to minimize hot spots. The data center's electrical power system contains an uninterruptible power supply with a diesel backup generator. The data center is protected with an FM-200 backed fire suppression system, which provides waterless fire suppression without leaving behind residue or particulates. Enhanced security measures are implemented to safeguard the equipment and the data within it. Security measures are enforced 24 hours a day, seven days a week, 365 days a year by a combination of on-premises security guards, University police officers, and video surveillance.

The data center has a virtualized environment. This environment consists of more than 415 virtual servers across 25 host servers. Virtualization provides key advantages: (1) High availability - in the event of hardware failure, virtual machines automatically restart on healthy resources, minimizing impact to end-users; (2) Flexible infrastructure - compute and storage is seamlessly scaled as current needs change; (3) Rapid deployment - new resources are provisioned on-demand.

Production servers running mission critical applications are clustered and configured for failover events across multiple clusters. Entire servers are backed-up to a dedicated infrastructure. The backup repositories are encrypted-at-rest using AES 256-bit encryption. The storage area networking applications, clusters, and switch-to-switch links are highly redundant. Incremental backups of data occur Monday through Friday. A full data backup occurs weekly. Full backups are sent off-site on a weekly basis to a secure secondary location. The data center currently manages over 125 terabytes of data.

Information systems are available 24/7/365 unless a scheduled maintenance period or mitigation of an unexpected event is required. Critical systems availability has exceeded 99.9% for the past 5 years.

Security, Support, Encryption and Confidentiality: The data center coordinates the network infrastructure and security with University Information Technology (UIT) at the University of Utah. This provides us with robust firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Centralized authentication and communication over public networks are encrypted using transport layer security (TLS) and/or virtual private network (VPN) technologies. Direct access to data center machines is only available while on premises or via a VPN client.

All network traffic is monitored for intrusion attempts. Security scans are regularly run against data center servers and IT staff are notified of intrusion alerts. Security is maintained with Windows user/group domain-level security. All files are protected at user/group levels and database security is handled in a similar manner with group-level access to databases, tables, and views. Finally, all laptops used by faculty and staff in the DCC are whole-disk encrypted.

The data center uses monitoring tools to continuously monitor applications and servers. Environmental and network systems are also monitored to ensure up-time. Members of the System Administrator team are on-call 24/7/365 to respond to urgent events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Participants Protection and Health Information Portability and Accountability Act (HIPAA) education and training. Security Awareness Training (SAT) is required annually. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems before access is provided.

Electronic Data Capture and Management: Extensive software resources are available in the DCC to support

its users, including:

- Electronic collaboration using eRoom™
- Electronic data capture systems (REDCap, Formedix Ryze, Twilio®)
- Database (SQL Server) and reporting infrastructure
- Query Management System
- Essential documents tracking software (Florence eBinder)
- Statistical software (SAS, R, SPSS, FACTS, PASS)
- Training software (Moodle)
- Business Intelligence and Analytics Software (Tableau).

Electronic Collaboration Support: eRoom™: The DCC has used eRoom™ to provide a “digital office” to support secure, efficient, confidential communication and collaboration among multiple users (>1200 current users) for over two decades. The software is Web-based and uses an office metaphor of rooms that may contain folders, documents, task lists, calendars, and task-oriented databases (Figure 2). The software is highly secure, and management of documents is intuitive.

The user can drag documents to and from their own desktop directly into the eRoom™ system. The system is optimized to integrate with standard office applications. We have used eRoom™ to support all aspects of our networks since their respective inceptions, including coordination of the Steering Committee and subcommittees, preparation of protocols, grants, manuscript preparation and publication, tracking Institutional Review Board (IRB) applications and approvals, and storage of scanned regulatory documents. eRoom™ provides significant efficiency, as it eliminates printing and mailing large paper documents. The system allows us to automatically notify study personnel of protocol changes, updates to Manuals of Operation, and important communications within any individual project. Investigator and research coordinator acceptance of eRoom™ has been enthusiastic and uniform in the > 140 multi-center studies we have coordinated.

Electronic Data Capture Systems

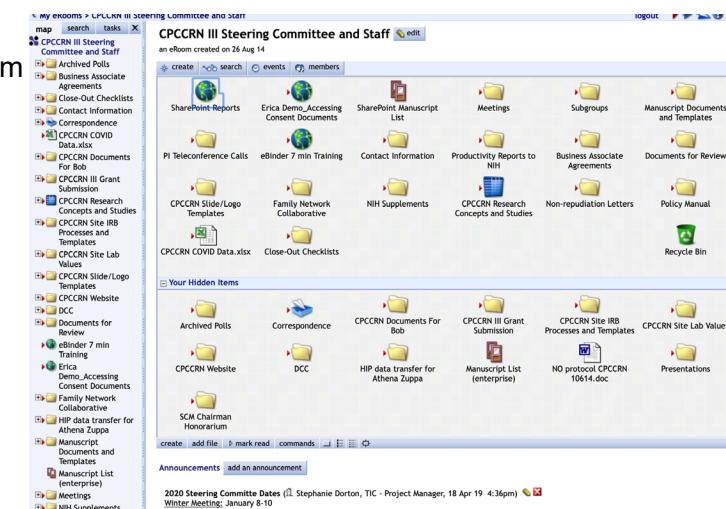
REDCap. REDCap is a secure web-based EDC system with robust features and advantages for participant-facing instruments such as eConsent or collection of patient reported outcomes. REDCap also has integration with a patient-facing application called MyCap. MyCap is a smart phone-based application that can be used by participants to provide information that is directly transmitted to the REDCap database. This app is available for Android and iOS platforms.

Formedix Ryze. Formedix Ryze is a clinical trial platform that stores metadata in a central repository, including datasets, forms, terminologies, files, and mappings. It also permits the Utah DCC to store its own standards and previous studies, enabling reuse as well as harmonization with nationally established vocabularies and terminologies. Reuse of successful file structures and use of common definitions improves efficiency. Entire studies can be built directly in this platform, and can then be exported to various electronic data capture (EDC) systems such as REDCap, which is described in the next section.

Formedix Ryze also has a dataset conversion feature that allows for generation of Study Data Tabulation Model (SDTM), Standard for Exchange of Nonclinical Data (SEND), and Analysis Data Model (ADaM) submission datasets, based on mapping created within the platform.

Twilio® We use Twilio®, a cloud communications platform, to send automated messages such as texts and email to research participants. We have used this technology to enable automated reminders and communication to participants, which encourages increased compliance with follow up data and participant retention. The technology also provides the ability to conduct remote data collection from a participant via SMS text or email.

SQL Server Database and Reporting Infrastructure

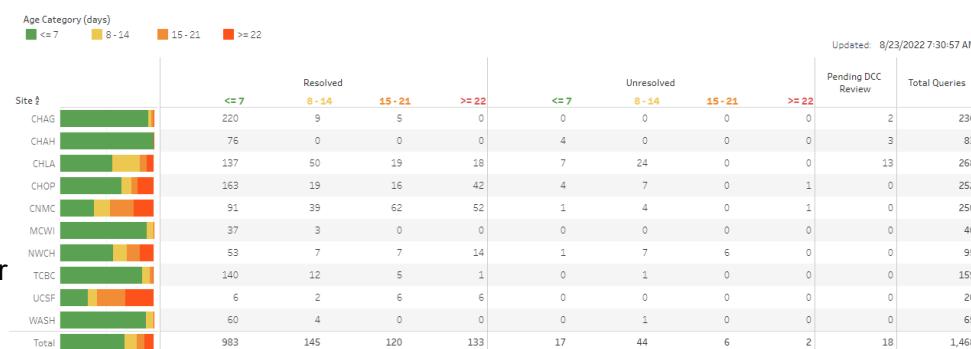


We use Microsoft SQL Server as our primary relational database management system (RDBMS) and have extensive experience (over 25 years) accessing the database from SAS, R, PHP, Perl, Python, and Java. Microsoft SQL Server provides sophisticated security facilities.

All study reports are based on data housed in the study data warehouse or study data marts, depending on the overall dataset size. A data mart is a simple, focused version of the data warehouse, and contains a repository of summarized data collected for analysis. The described architecture contributes to streamlined, efficient data processing for frequently refreshed reports.

We adopt a defense-in-depth approach to information security. All data are encrypted in-transit across communication channels using currently supported version of Transport Layer Security (TLS). Authentication, authorization, and encryption at-rest are implemented using the Windows Data Protection application programming interface (API). Data warehouses, databases, and data marts are only accessible on-premises at the Utah DCC or with an established VPN.

Query Management System: While EDC systems such as REDCap have data field validation, sophisticated validation of data between different forms requires processing after data are submitted to the Utah DCC. We have written a Java-based application called the Query Management System and have used it successfully for 20 years to manage all queries for data discrepancies. The clinical data manager determines the business (validation) rules for each data element, and SQL queries are written to enforce each rule. The system executes during the night, identifies all new data discrepancies, and creates a single email to each site research coordinator that contains all the new discrepancies. Discrepancies are not repeated in email notification for seven days, a feature appreciated by research coordinators. Most importantly, if the data discrepancy is corrected in the EDC by the site research coordinator, the system automatically resolves the query without requiring DCC staff intervention. The Query Management System does *not* have read or write access to the EDC, and all data entry by sites is done via the EDC system. If the research coordinator needs to communicate with the clinical data manager and request manual resolution, this is also done through the system, so a complete audit trail is available for all data element changes and query resolutions.



Study investigators, research coordinators, and NIH staff can view real time reports by specific clinical sites or individual query rules, by date of occurrence and resolution, or by aging of queries (Figure 3). This software provides a powerful management tool for monitoring data quality in networks or trials that we coordinate. Finally, the system maintains an audit trail of all queries, query communications, and query resolution.

Essential Documents Tracking Software We offer Florence eBinder to track essential documents at each site. Sites upload essential documents into this 21 CFR §11 compliant system, which fully supports electronic signatures. We require documentation of letters of non-repudiation with the FDA to fulfill requirements for electronic signatures.

Statistical Software We use SAS Version 9.4 as our primary statistical software for data preparation and analysis. We also utilize R for statistical work when appropriate. Other statistical packages are also utilized when specific features or capabilities not readily satisfied by our standard software are needed. We consider SAS to be most appropriate for trials that are subject to an investigational new drug (IND) application, as SAS has documentation to support its validation, while R is highly customizable by end users.

Online Training Software: The Utah DCC offers the use of Moodle, an open-source free software product, to support online learning by investigational site personnel. Audio and video presentations can be embedded in the curriculum. Figure 4a provides an example of modules addressing workflow in a previous study PEACE(AZ). A screenshot of the first module is also provided in Figure 4b. The user can start and stop the presentation at will, and at the end of the presentation, a quiz is provided. The software tracks individual users, and certificates

are issued when a user has completed all the lessons and passed all the quizzes. We believe that online training is critical to complement training that occurs at investigator meetings and is particularly valuable in the context of research coordinators at multiple sites because of routine staff turnover.

The figure consists of two screenshots of a Moodle-based online study training system.
 (a) List of Moodle modules for PEACE(AZ) Study: This screenshot shows a list of four modules under the 'PEACE(AZ)' course. Each module has a title, a brief description, and a progress bar. The modules are: 1. PEACE(AZ) Workflow and Database Training: Module 1 (You are expected to have read the protocol prior to reviewing these modules), 2. PEACE(AZ) Workflow and Database Training: Module 2 (You are required to view module 1 prior to viewing this module), 3. PEACE(AZ) Workflow and Database Training: Module 3 (You are required to view modules 1 and 2 prior to viewing this module), and 4. PEACE(AZ) Workflow and Database Training: Module 4 (You are required to view modules 1, 2 and 3 prior to viewing this module).
 (b) Module 1 presentation: This screenshot shows the content of Module 1. It features a large title 'PEACE(AZ) Workflow and Database Training: Module 1' and a subtitle 'Stephanie Bisping, BSN, RN, CCRP Collaborative Pediatric Critical Care Research Network'. Below the title, there is a section titled 'Navigation' with links to 'My home', 'Site pages', 'My profile', 'My courses', and 'Courses'. There is also a 'Recent activity' section showing activity since April 13, 2014, and a 'Settings' sidebar.

(a) List of Moodle modules for PEACE(AZ) Study (b) Module 1 presentation

Figure 4: Example online study training with Moodle system.

Document Typesetting Software

We use an innovative system for producing Study Protocols, Manuals of Operation, and Clinical Study Reports (CSR) using open-source typesetting software (\LaTeX). Template macros are developed for specific aims, inclusion and exclusion criteria, study outcomes, and hypotheses of individual studies. These macros are then used throughout documents to assure consistency throughout protocols and manuals. Boilerplate macros have been developed for IT security descriptions, FDA and other Federal regulatory requirements, HIPAA requirements, record retention, inclusion of women and minorities, and inclusion of children sections of protocols. Finally, an overall protocol template has been created, and the protocol is automatically integrated into the Manual of Operation, assuring consistency between the protocol and the Manual. The output of our typesetting system is a versioned PDF document that discourages direct editing by individual sites or research staff. This process provides assurance that the protocol is identical throughout the sites of a multi-center study.

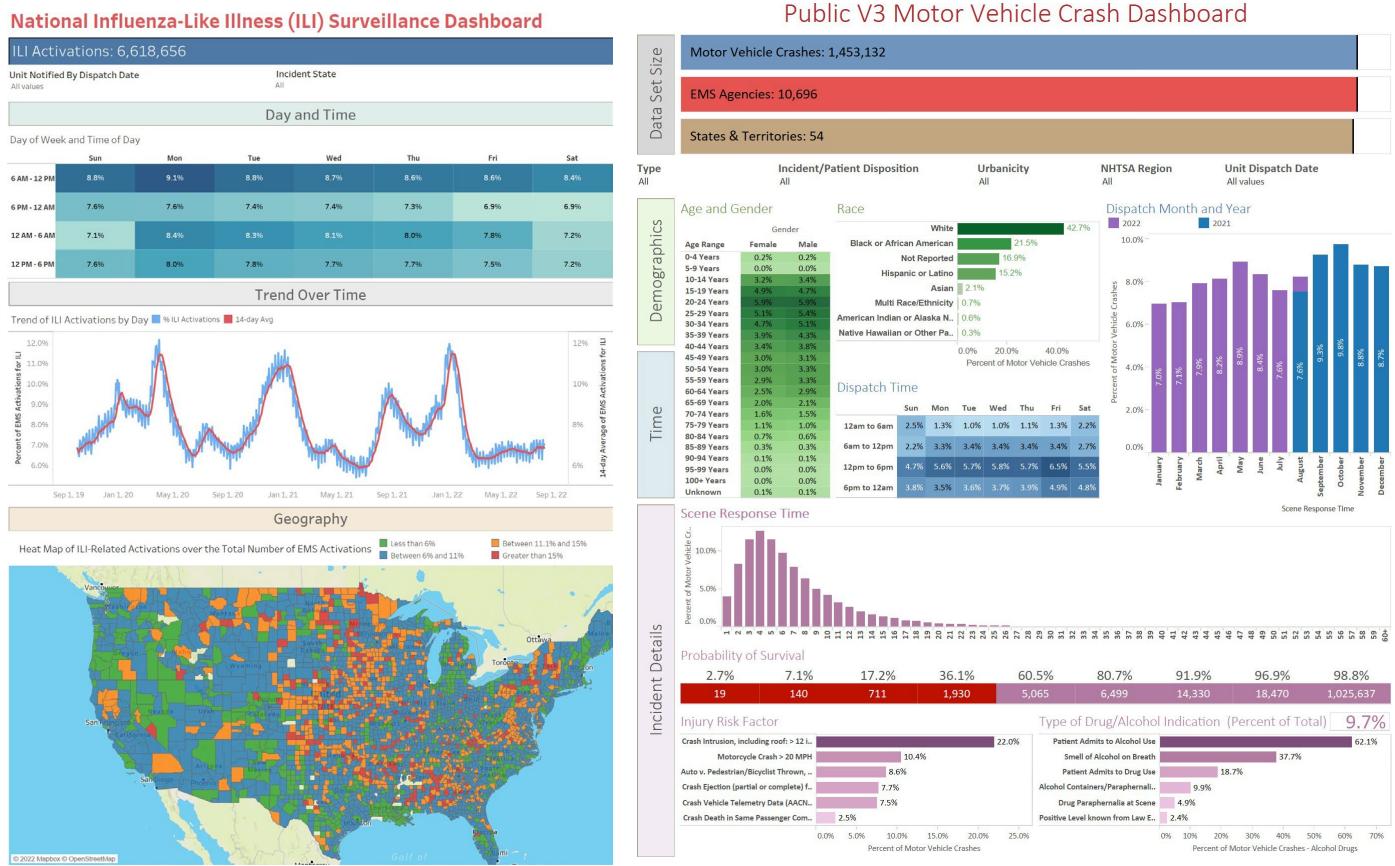
Prior to creating this system, documents were prepared using common word processing software, and iterative interactions with study investigators consumed months of time. We discovered that individual investigators subsequently altered the protocol in seemingly reasonable ways, such as adding the names of institutions, attempting to clarify issues in response to IRB review, and other changes. Unfortunately, these types of edits at multiple institutions can endanger the scientific value of a multi-center study. Our document typesetting system has eliminated this vulnerability and allows strict source control over the protocol and associated documents to be maintained.

Business Intelligence and Analytics Software

The Utah DCC has extensive experience producing interactive dashboards on our website for public and government partners. An illustrative example from the NEMSIS TAC describes these capabilities. The NEMSIS TAC is hosted at the Utah DCC and facilitates, enables, and promotes the implementation and use of the National EMS Data Repository through maintaining and supporting forward-facing services and tools. These include reports, dashboards, multi-dimensional Online Analytical Processing (OLAP) cubes, annual Public-Release Research Datasets, and direct research assistance. The Utah DCC uses Tableau, Power BI, and SQL Server Reporting Services (SSRS) for data analysis and business intelligence. By leveraging these visualization tools, we can create interactive dashboards, allowing viewers to filter datasets on variables of interest and export the data in easily consumable formats. In the cases of NEMSIS, reports are generated for EMS stakeholders through Tableau dashboards using repository data. The reports are refreshed with current data on an hourly, daily, or monthly basis. In some cases, we have collected and displayed real-time, surveillance-level data. Users can subscribe to email push notifications from certain reports for current information delivered directly to their

email. Dashboards provide an accessible way for users of all experience levels to interact with a tremendous amount of data in near-real time; illustrative examples are shown in Figure 5. Access to dashboards can be restricted to specific user groups based on the data shared and who is authorized to view and utilize that level of information. We have also designed dashboards to provide review of longitudinal data trends. Informed by our experience with the NEMESIS TAC project multiple levels of access can be provided, from public-facing, investigator, NIH, or other. Authorized users are granted permissions to reports and dashboards through layered security, which includes an approved Active Directory (AD) account and report-level permissions within the reporting tool.

Figure 5: Examples of dashboards designed using Tableau.



(a) Example from influenza-like illness

(b) Example from motor-vehicle crashes

Tableau allows for the consolidation of study data and translation of that data into information provided in real-time to authorized users involved with the multi-center study. In our research networks, we permit every investigator, research coordinator, and other research staff to access these read-only reports. Our reports include overall and site-specific performance metric reports, study demographics, and enrollment and data quality reports. An example of study accrual information is provided in Figure 6 on next page.

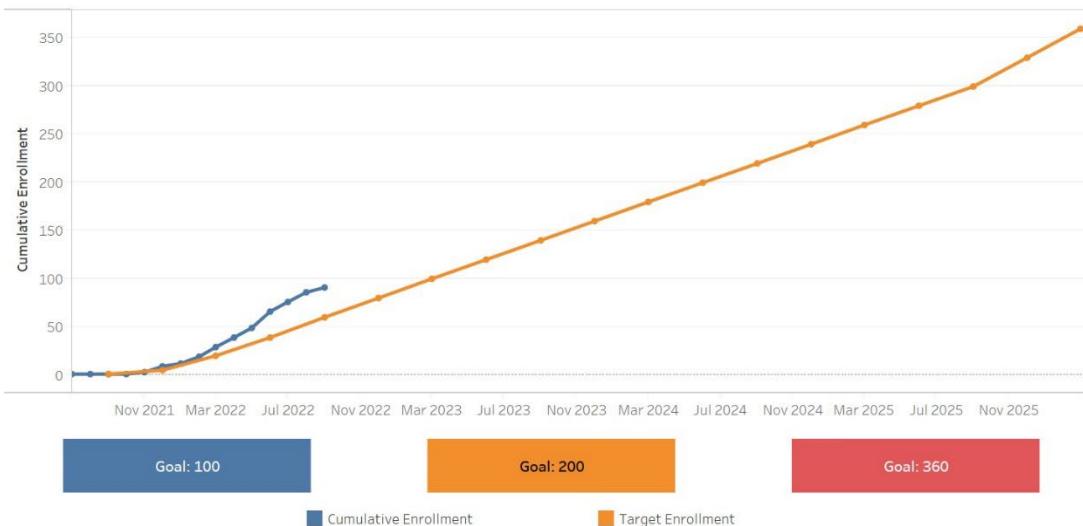
STArT Study Level Enrollment

Last Updated: 8/26/2022 7:30:45 AM

Study Details

Study Full Name	Sickle Cell Disease Treatment with Arginine Therapy Trial (STArT)
Enrollment Start Date	June 21, 2021
Target Enrollment End Date	February 28, 2026
Enrolled	91 Participants
Target Sample Size	360 Participants
Enrollment Rate per Month	7 Participants/Month
Target Enrollment Rate per Month	6 Participants/Month
To meet enrollment target date, you need to enroll	7 Participants/Month
At the current rate you will finish enrolling on	02/20/2026

Cumulative vs. Target Enrollment Plot



Current Enrollment

	Screened	Preliminarily Eligible	Approached for Con..	Consent	Eligible to be Rando..	Randomized	Withdrawn
Total	1,077	459 (42.6%)	278 (60.6%)	95 (34.2%)	93 (97.9%)	91 (97.8%)	0 (0.0%)

Screened – The number of participants who met inclusion criteria.

Preliminarily Eligible – Preliminarily Eligible is the number of participants who met initial eligibility criteria. Preliminarily eligible percentages are out of the number of screened participants per site.

Approached for Consent – Approached for consent percentages are out of the number of preliminarily eligible participants per site.

Consent – Consented percentages are out of the number of approached participants per site.

Eligible to be Randomized – Eligible to be randomized are the number of participants who met all eligibility criteria, CMP reviewed and were eligible to be randomized.

Eligible to be randomized percentages are out of the number of consented participants per site.

Randomized – Randomized percentages are out of the number of eligible to randomized participants per site. Withdrawn – Withdrawn percentages are out of the number of randomized participants per site.

The default setting for all reports displays all sites and includes the entire duration of each study. The reports are purposefully not anonymized, as we have found that transparency about site performance, for example enrollment and retention, enables the sharing of best practices from high performing sites, and the opportunity for improvement for sites performing at a lower level. An important feature of these reports is the ability for users to customize the date range and sites included in the report, which allows a site to compare its performance at different time points in a study.

Website Creation and Maintenance

We use WordPress, which is a free and open-source content management system written in PHP to develop and maintain both public-facing and secure websites. The Utah DCC-supported websites include mobile-optimized design, contain consistent typography, are optimized for speed, contain Search Engine Optimized (SEO) elements, are compatible cross-browsers, and are intuitive to navigate. We leverage WordPress plugins to provide feature-rich sites, such as the ability to present relevant publications and scholarly articles data from Zotero in real-time through the Zotpress plugin. Websites are hosted on-premises in the Utah DCC data center. All sites are configured with the currently supported version of TLS (1.3 and 1.2 at time of writing). We adopt Mozilla's Intermediate configuration for cipher suites, which includes Forward Secrecy and Authentication.

Clinical Data Management: The Utah DCC offers comprehensive clinical data management services beginning at protocol development and carried through to study closeout. The major components of our data management

approach are outlined in Figure 7. We use systems and processes to adhere to the Society for Clinical Data Management's Good Clinical Data Management Practice©.

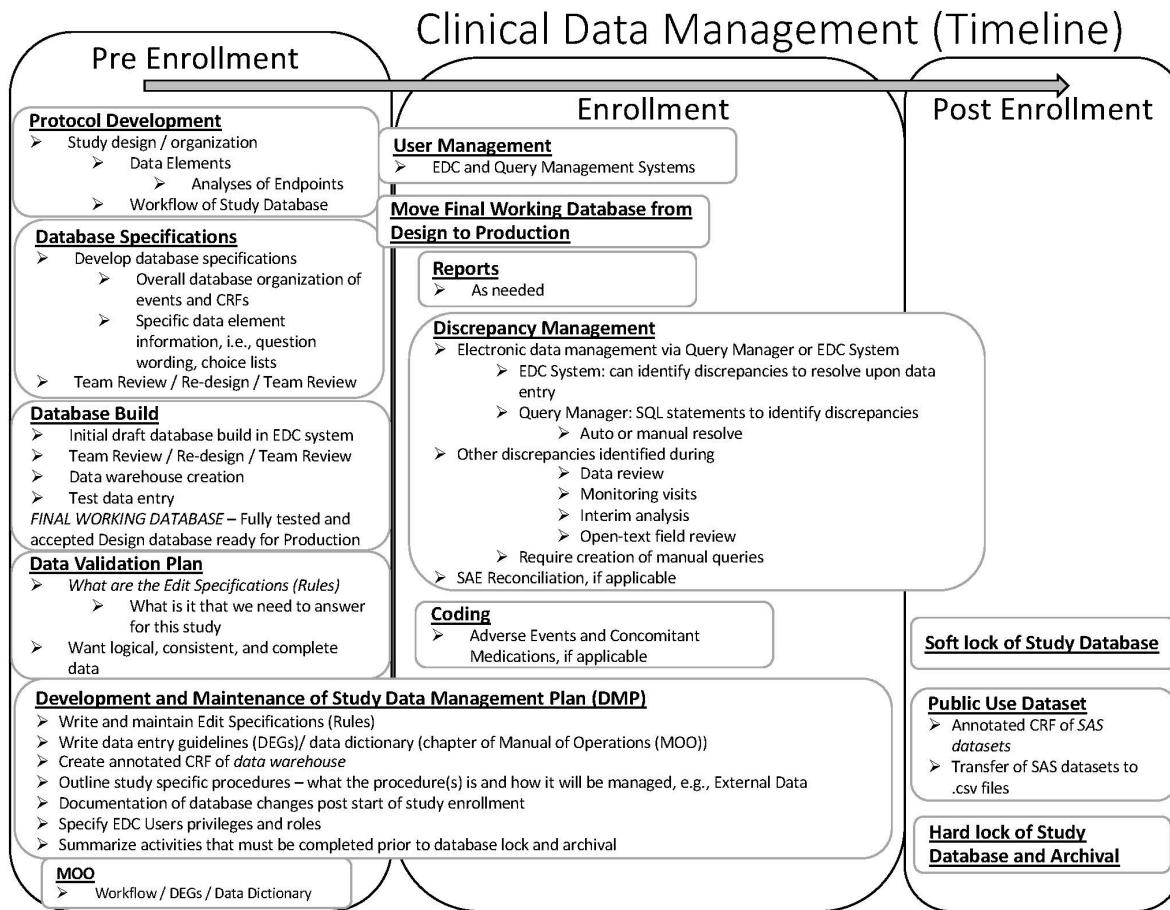


Figure 7: Clinical data management activities across entire study timeline.

Roles Across the Study Timeline

Data Definitions. CDM study participation begins during protocol development in order to provide insight on study events, workflow, and data elements. Data elements and definitions are generated based on the study protocol and in consultation with study PIs, informatics and biostatistics faculty, and other study staff. Key data elements are identified in consultation with study statisticians and in conjunction with the development of the Statistical Analysis Plan (SAP). Data elements are then organized into data collection forms for each planned study event. CDMs provide expertise and insight on how the desired data elements can be collected to fit within clinical and study workflows.

Data Harmonization. CDMs use standardized tools such as forms, variable definitions, and choice sets whenever feasible to facilitate consistency across studies. Several standard forms have been created for common forms such as demographics and adverse events. Greater work is being done to align variable choice sets with controlled terminologies and align data collection to Clinical Data Interchange Standards Consortium (CDISC), Logical Observation Identifiers Names and Codes (LOINC), and other national standards. Extensive work in harmonizing data elements has been undertaken in collaboration with NIH staff within the Helping to End Addiction Long-Term (HEAL) initiative.

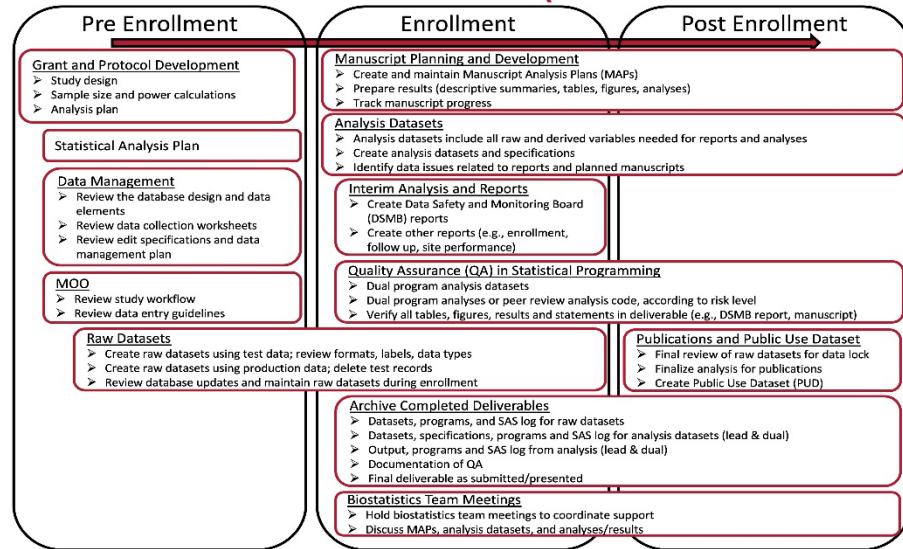
Database Development. Database development begins as early as is feasible for each study. In consultation with the Director of Clinical Data Management, an appropriate EDC system is selected for each study. Once the EDC is selected, the CDM begins work on the database specifications that detail the overall database organization (events and forms) as well as all information relating to the data elements (e.g., variable names, question wording, choice options). In tandem with the development of database specifications, the CDM builds a draft database within the EDC. Study PI and staff input from review and testing is incorporated to develop a final study database.

Data Monitoring: CDMs are heavily involved in data monitoring to ensure accurate and complete study data. CDMs use validation checks within each EDC as well as an in-house developed application, Query Manager, to write rules that regularly run against the data entered into the EDC. These rules range from checking completeness, missingness, or out of range values to complex queries written using SQL. The CDMs work closely with the statistical team to identify key rules that are needed. Additionally, CDMs participate in a risk assessment for each study. This risk assessment helps identify data elements and study aspects that require additional monitoring. CDMs help develop reports for monitoring these risks and participate in communicating issues found to study staff.

Statistical Design and Support: Statistical support is provided throughout the life of each study. The major aspects of our statistical support are outlined in Figure 8 below.

Statistical support begins as early as possible. The faculty statistician provides input on study design, sample size and power, and the analysis plan. During protocol development, statisticians review and provide feedback to ensure that key outcomes and data elements needed for analyses are appropriately identified and collected. The Statistical Analysis Plan (SAP) is written to detail analyses for protocol aims and is a key document in ensuring that correct data are collected.

BIOSTATISTICS SUPPORT (STUDY TIMELINE)



Statistical Analyses

Standards. Specific quality control procedures are used by staff statisticians to ensure statistical work is accurate. Detailed analysis dataset specifications are created for each analysis dataset and used to independently program all variables to be used in analyses. At a minimum, programs for statistical output undergo code review by a second statistician. For higher risk analyses, the output is independently programmed by a second statistician.

Accelerating Analyses and Publication. Statisticians begin work on manuscripts early in the study to accelerate the publication of results. Prior to enrollment or shortly after enrollment has started, statisticians consult with study PIs to identify primary and second manuscripts to be written. For each manuscript, the PI or lead author completes a Manuscript Request Form (MARF). The MARF is then used by the statistician to create a detailed Manuscript Analysis Plan (MAP). All datasets, analyses, and tables/figures are identified in the MAP and programs to generate them are prepared. Once data collection is complete, the process to generate results simply requires the running of previously created programs. In the recent NIH-supported PECARN Probiotics trial,¹⁶⁶ the Utah DCC was able to release statistical reports for 12 manuscripts immediately following data lock.

Data/Observational and Safety Monitoring Boards. For studies that require a Data/Observational and Safety Monitoring Boards (DSMB/OSMB), a mock report is created once the study database is complete. The SAP and mock DSMB/OSMB report are used to begin work on the creation of analysis datasets and the full report. For each DSMB/OSMB meeting a detailed timeline is created to ensure that adequate time is provided for the cleaning and locking of data, creation of the report, and quality control of all statistical work.

Planning for CDISC and other Submission Standards

Utah DCC statisticians have received training in CDISC standards. As needed for specific studies, statisticians review data elements for conformance to NIH common data elements, NCI controlled terminology, domain core elements, and other appropriate standards to facilitate adherence to public-use dataset submission standards, FAIR (findable, accessible, interoperable, and reusable) principles, and standards for submission to CDISC SDTM as appropriate for each study. For studies that require CDISC, statistical staff are assigned to lead this work.

Project Management Professionals

Utah DCC clinical PMs are responsible for the planning and execution of projects. PMs are engaged for the entirety of the study, from study startup through closure. Most DCC PMs have a background in clinical research. The Utah DCC Project Management Office (PMO) provides a separate, certified Project Management Professional (PMP) to each study to complement the clinical project managers. The PMP certification is the gold standard in project management, and it is recognized as the industry standard to validate competence and expertise.

The PMP team is supervised by Lisa Young, whose capabilities and expertise are previously described. Diane Hartford, MS, PMP leads the IT PMO at the Utah DCC and is the Senior IT Project Manager for complex IT and clinical projects. She has a master's degree and 20 years of project management experience and is a certified PMP. Ms. Hartford and her team support numerous projects, recently including the NIH's HEAL Core Common Data Elements (CDE) Initiative by tracking PI submissions, improving processes, and reviewing CDE measures. Other projects include migrating the NEMSIS databank and systems from on-premises to the AWS Cloud. She directs budgeting, procurement of professional services, and tracking and reporting the progress of internal teams and external organizations.

PMPs are core members of the study team, and they partner closely with clinical PMs to organize the work performed by the study team. During study startup, the PMP and clinical PM develop the project plan, which includes decomposing milestones into deliverables and deliverables into the smallest unit of work. These tasks are assigned to CDMs, biostatisticians, faculty biostatisticians, IT staff, PIs, and other study team members. Predecessors and dependencies are identified and managed in the project plan (Figure 9). Once the project plan is developed, the PMP leads the activity of identifying the critical path, which is the longest sequence of tasks that must be finished to complete a project. With the finalized plan, the PMP tracks the status of each task, adjusting duration and dates as needed. Other key project management activities include removing barriers to progress and communicating project status to the stakeholders (Figure 10).

Role of Project Management Office

The PMPs are part of the PMO, which provides governance across the portfolio of projects at the Utah DCC. The PMO maintains an enterprise view of all projects, which allows for a top-down strategic alignment and improves our ability to allocate resources effectively. PMPs are trained to design, develop, and implement projects using standardized tools and methods. They utilize PMO-provided templates for status reports, Gantt charts, project plans, communication plans, and stakeholder engagement plans. Standardizing the project management approach enables consistent and accurate results.

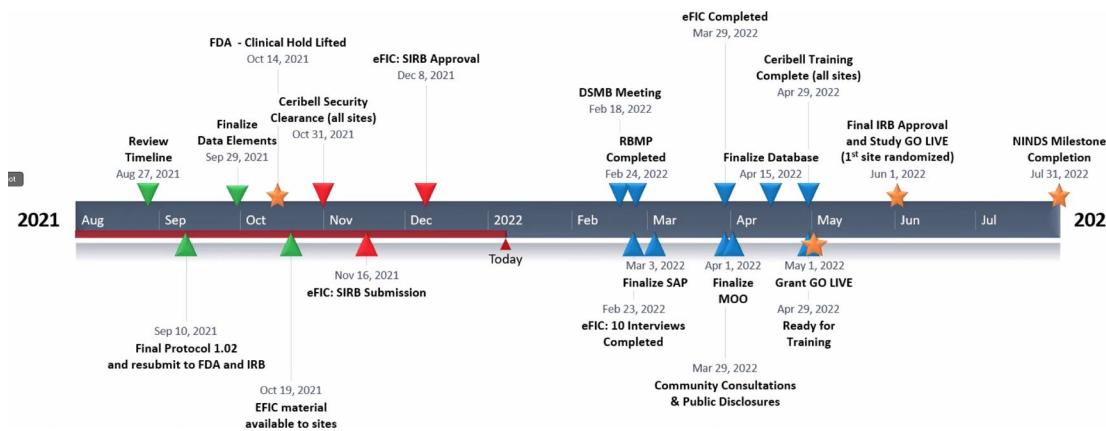


Figure 9: Example study timeline with milestones.

% Complete	Task Name	Duration	Start	Finish	Predecessors	Resource Names
100%	▪ Statistical Analysis Plan (SAP)	211 days	Thu 4/15/21	Thu 3/3/22		
100%	Statistical Planning Meeting (kick-off)	0 days	Thu 4/15/21	Thu 4/15/21		Mark,John
100%	Draft SAP	15 days	Fri 12/10/21	Thu 1/13/22	43,16,75	John,Rich
100%	Review by internal study team	5 days	Fri 1/14/22	Fri 1/21/22	44	Internal Study
100%	Review and approval by study PIs	5 days	Fri 1/14/22	Fri 1/28/22	44	Mark,Pete,Athena
100%	Incorporate Feedback	5 days	Mon 1/31/22	Fri 2/4/22	46	John
100%	Cross reference SAP to database	5 days	Mon 2/7/22	Fri 2/11/22	47SS,84	Russ,Bobby
100%	Send to DSBM for optional review	10 days	Mon 2/14/22	Mon 2/28/22	48	John,DSBM
100%	Incorporate	2 days	Tue 3/1/22	Wed 3/2/22	49	John
100%	Final SAP	1 day	Thu 3/3/22	Thu 3/3/22	50	John,Mark,Pete,Athena
100%	▪ Data Management Plan	1 day?	Fri 11/1/19	Fri 11/1/19		
100%	Draft initial study DMP	10 days	Fri 11/1/19	Thu 11/14/19		
100%	DMP Review	8 days	Fri 9/3/21	Wed 9/15/21		
100%	Final study DMP	5 days	Thu 9/16/21	Wed 9/22/21	54	

Figure 10: Example study workplan for a statistical analysis plan (SAP).

Regulatory Affairs and Quality Assurance

The Regulatory Affairs, Compliance, and Quality team is led by Director of Research Amy Goodman, PhD, who directs teammates Maryse Brulette, BPharm, DESS, CCRA and Shelly Roalstad, MS. This team is charged with developing, piloting, and testing quality improvements and innovations across studies and ensuring that all Standard Operating Procedures (SOP) are in compliance with current regulatory requirements. This cycle is an essential part of our Quality-by-Design initiative, an enterprise-wide approach to building quality into clinical research from start to finish.

International Conference on Harmonization (ICH) guidelines and regulatory guidance have evolved to encourage more efficient approaches to clinical study planning and execution. In response, the Regulatory Affairs and Quality Assurance team efforts focus teams on risk-based approaches to manage key data, processes, and systems that continue to ensure human participant protections and reliability of study results.

The team is a highly visible endeavor in the Utah DCC, working closely with study teams to provide guidance and hands-on support to integrate quality approaches into each study. These activities include proactive risk assessment, risk management planning, and execution of risk management activities that begin during protocol development and continue through study duration.

Based on our experience with the AQC, we have developed our approach to Risk Assessment and Mitigation, consistent with the ICH Good Clinical



Practice (GCP) E6(R2) process to use risk-based monitoring strategies (Figure 11 above). We are abreast of and adapting to ongoing ICH GCP E6, E8 and E3 revisions.

Standard risks include data entry errors, missing data, loss to follow up, and other risks that are commonly associated with multi-center studies, are sometimes not critical to human participant protection or reliability of study results and are handled by relatively routine clinical research operations and training. Missing data and loss to follow up are critical to study reliability, but these are known risks that we will always attempt to mitigate. We identify heightened and critical risks that are specific for each study and focus our training and monitoring processes around these risks. We use the approach of identifying the risk, estimating the likelihood, impact, and detectability, and calculating a risk score. We quantify Key Risk Indicators (KRI) that will be measured and monitored during study implementation. The individual roles and responsibilities of the DCC team in monitoring KRI status are established prior to beginning enrollment. Finally, we develop a mitigation plan targeted to the specific risk.

As an example, we identified 15 to 20 heightened or critical risks for a recent trial that assigns study arms based on a laboratory-based immunophenotype, and Figure 12 illustrates the approach with four risks that are specific to this trial. The top row identifies “Miscommunication of Phenotype” as a critical risk, assumed to be rare, but of

very high impact. This risk could result in a research participant being assigned to the wrong clinical trial. The mitigation plan will be to have two investigators verify the phenotype, and for two individuals at the enrolling clinical site verify the proper values before randomizing the participant. The other rows demonstrate the approach with three other identified risks.

This approach to risk identification, assessment and mitigation has been transformative for the industry, and moves away from trying to identify every possible, but perhaps less important, data entry error (for example, date sequences) on a large number of data elements. By adopting this approach, we can focus our physical and central site monitoring, and training, for clinical sites on heightened and critical risks to each trial, to assure that human participants are well protected, and the trial results are valid and reliable.

Preparation of Public-Use Datasets

To meet the NIH Data management and sharing plan requirements and to facilitate data transparency and make data more publicly available, Utah DCC staff create a public-use dataset (PUD) after completion of each study and publication of primary results. Project Management, Clinical Data Management, and Biostatistics staff jointly work to de-identify study data and prepare these data for sharing. We have shared multiple datasets previously for our federally funded studies.

De-identification involves randomly generating a new ID for each participant, recoding variables as needed, and removal or redaction of open text fields to remove PHI. Accompanying documentation (e.g., study protocol, annotated electronic case report forms) is updated to provide guidance to researchers that utilize the PUD. All shareable PUD materials are reviewed and approved by study investigators prior to deposit in a suitable repository. Our data sharing plan will include data type, method of sharing, data access, and sharing processes.

	Risk Short Name	Research Component	Risk Description	Risk Category	Likelihood	Impact	Risk Score	Detectability	Key Risk Indicator	Mitigation Plan
8	Miscommunication of Phenotype	07. Randomization	Intention to treat requires subject to stay in arm to which they were randomized. If a subject is erroneously randomized to the wrong arm, statistical significance may be adversely effected.	Critical	2 Rare	5 High	10	1 Highly Detectable	KRI = # of patients that were randomized to the wrong phenotype per quarter	Have a double verification of lab values so that two investigators determine the appropriate phenotype. Have two staff members verify the proper values to input into the randomization program.
9	Lab Shipping Error	08. Interventions and/or Procedures	Laboratory samples must be sent overnight in order to analyze the sample accurately. Delays or other errors in shipping could lead to a missed subjects or erroneous laboratory results.	Heightened	4 Very Probable	4 Moderate-high	16	2 Very Detectable	KRI = # of shipping errors per quarter	Train staff to properly ship samples. Implement a quality control check at each site to ensure the addresses on the shipping labels are correct and the shipping box is packaged correctly.
10	Lab Processing Error	08. Interventions and/or Procedures	If the laboratory sample isn't processed correctly or expired LPS tubes are used, erroneous results may be obtained leading to erroneous randomization.	Heightened	3 Probable	5 High	15	4 Slightly Detectable	KRI = # of lab processing errors per quarter	Have NWCH staff review expiration dates on incoming tubes. Have sites maintain a log with expiration dates and check on a weekly basis. Have a laboratory manual available at every site to ensure easy access to laboratory processing materials. Implement an easy-to-follow, simplified flowsheet that shows all major steps to processing samples.
11	Lost to follow-up	08. Interventions and/or Procedures	Specific Aim 1 relies on outcome data. If participants are lost to follow-up, main endpoint cannot be obtained.	Critical	4 Very Probable	5 High	20	2 Very Detectable	KRI = # of lost to follow-up subjects each quarter	Implement MyCap to help keep participant engaged. Provide a follow-up card to participants prior to discharge. Consult the Recruitment Innovation Center at Vanderbilt University to provide additional retention strategies.
										Train the RCs regarding the importance of obtaining

Figure 12: Heightened and critical risk assessment for immunomodulation trial.

Standard Operating Procedures

The University of Utah has SOPs for all clinical research at the University. These were developed by Utah DCC staff working with the contact PI of this proposal and are now publicly posted on the Vice President for Research website at <https://qualitycompliance.research.utah.edu>. These SOPs include the following:

- UU SOP - 1 Standard Operating Procedure Process
- UU SOP - 2 FDA Inspections
- UU SOP - 3 Protocol Training for Investigator and Study Staff
- UU SOP - 4 Investigator Responsibilities
- UU SOP - 5 Delegation of Authority
- UU SOP - 6 Study Records Management
- UU SOP - 7 Deviations: Documentation and Reporting
- UU SOP - 8 Obtaining Written Informed Consent

- UU SOP - 9 Case Report Form Completion Standards
- UU SOP - 10 Monitoring Visits for Externally Sponsored Clinical Trials
- UU SOP - 11 Investigational New Drug Application in FDA-Regulated Research
- UU SOP - 12 Investigational Device Exemption Applications in FDA-Regulated Research
- UU SOP - 14 Safety Assessment and Reporting

The Utah DCC has additional relevant Standard Operating Procedures including:

- UU-DCC-SOP-PD-303 - Risk Assessment and Risk Management System
- UU-DCC-SOP-CO-506 - Investigator Compliance Oversight
- UU-DCC-SOP-GA-103 - Clinical Research Training
- UU-DCC-SOP-GA-104 - Conversion of Original Signed Paper Records to Electronic Records
- UU-DCC-SOP-DM-701 - Clinical Data Management
- UU-DCC-SOP-DM-702 - Use of Electronic Data Management Systems

Regulatory Support

The Utah DCC has significant experience providing regulatory services and guidance for federally and industry-funded clinical research. Our areas of expertise include but are not limited to:

Advising and partnering with investigators regarding FDA meetings and strategy regarding IND and Investigational Device Exemption (IDE) submissions. The University of Utah has staff members and resources to assist with IND and IDE submissions, and the DCC has assisted multiple investigators with IND and IDE submissions, including strategies for early discussions with the FDA. Our leadership includes personnel who have served on FDA advisory committees (Dr. Dwyer), and who have collaborated on IND (Drs. Dwyer and Goodman) and IDE (Drs. Dwyer and Goodman) submissions with academic and industry partners. Our team has the capability to assist with and can provide expertise on strategic discussions with the FDA, should these become part of the DCC's role as new ancillary projects are proposed.

Consent Builder. The Utah DCC has created an innovative Consent Builder application that locks the primary consent text and then constructs the local text from information entered by sites into a REDCap database. Site-specific documents are automatically generated as PDF documents for each site. The Consent Builder is particularly valuable when amendments are made to the primary part, as all the documents can be automatically regenerated for all sites in minutes instead of weeks.

Collection and maintenance of essential documents. The DCC offers both turnkey and custom solutions for the collection and maintenance of essential documents, which are enforced for all studies. eRoom is available for all studies, and Florence eBinder is available for tracking essential documents in a 21 CFR §11 compliant system. Sites in ongoing studies have filed letters of non-repudiation with the FDA to fulfill the requirements for electronic signatures.

GCP training. The Utah DCC offers extensive GCP training for study sites and investigators. GCP lectures are customized to each specific study, and educational scenarios are provided to illustrate key issues likely to be encountered during the study conduct. Lessons learned on application of regulations and methods of handling challenging regulatory situations are shared in monthly webinars and study newsletters.

Medical Monitoring and Adverse Events (AE). AEs are consistently collected using standardized definitions and MedDRA coding is utilized. We provide services for medical monitoring of study data across a number of domains. Our team has an established workflow for reporting serious adverse events (SAE) that assures rapid evaluation of SAEs at the DCC, and we have built SAE review directly into our EDC system. Furthermore, we provide investigator training in SAE reporting, and we can provide support to sites in evaluating and reporting AEs. While we do not anticipate a large burden of AE reporting in this cohort study, we have the capability if future interventional trials are incorporated into this network.

Risk-Based Monitoring. The Utah DCC has developed a standard Risk-Based Monitoring Plan that can be customized based on study risk (Section A.7.3). Our team has expertise in remote monitoring and in particular, risk-based monitoring of both regulatory and data elements of studies.

Validated EDC databases. The Utah DCC offers access to a validated and 21 CFR §11 compliant EDC database for use in FDA-regulated clinical trials.

ClinicalTrials.gov. The Utah DCC has the expertise to advise on and manage ClinicalTrials.gov entries, ensuring entries are updated as required, including dissemination of results.

University of Utah Institutional Review Board

The organizational chart of the IRB is shown in Figure 13.

Ann Johnson, PhD, MPH, CIP is the Director for the University of Utah Institutional Review Board (IRB) and Human Research Protection Program (HRPP), as well as an adjunct faculty member in the University of Utah College of Nursing. She specializes in research ethics and is an expert in human participants research regulations and requirements. She has been a leader in establishing a single IRB (sIRB) process for the University of Utah and provided SIRB leadership throughout the TIN. She is an active member of the research community, not only reviewing and auditing proposals for the IRB, but also having conducted research in the fields of public health and research ethics. She has taught undergraduate- and graduate-level courses and is instrumental in continuing research education for the University of Utah. She also serves as a site visitor for the Association for the Accreditation of Human Research Protection Programs.

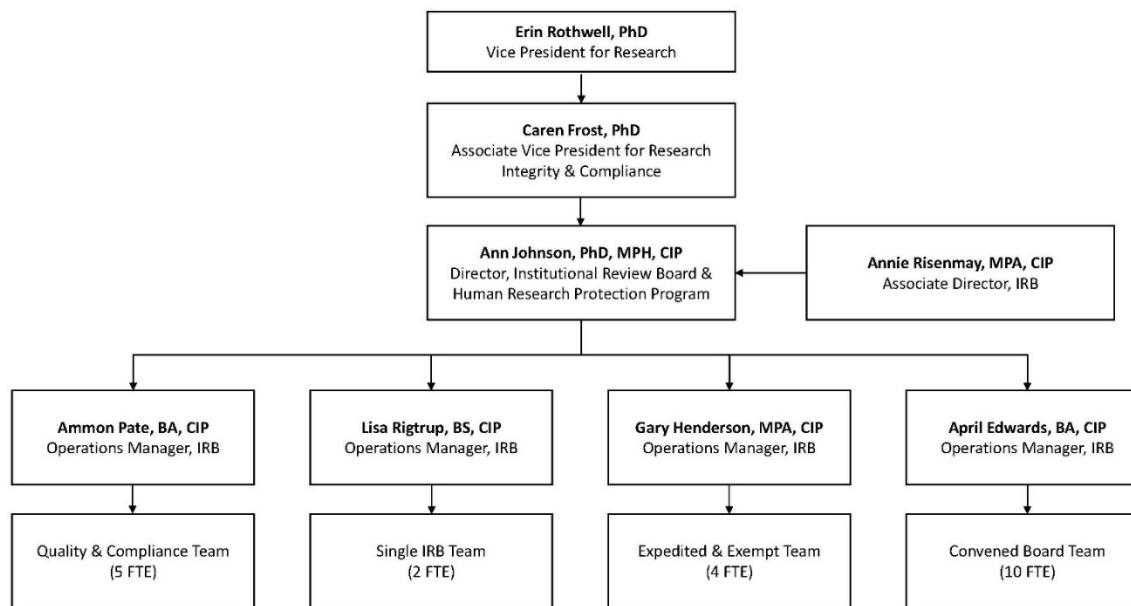


Figure 13: Organizational chart of University of Utah IRB.

Description and Scope of Activities

The University of Utah has an active Federal-wide Assurance (FWA) with the Office for Human Research Protections (FWA00003745) and agrees to apply 45 CFR §46 whenever the University "becomes engaged in human participants research conducted or supported by any U.S. federal department or agency that has adopted the U.S. Federal Policy for the Protection of Human Subjects (also known as the Common Rule), unless the research is otherwise exempt from the requirements of the Common Rule or the department or agency conducting or supporting the research determines that the research shall be conducted under a separate assurance."

The University IRB and Human Research Protection Program (HRPP) adheres to 21 CFR §50 and §56 as well as other parts of 21 CFR as appropriate for clinical investigations regulated by the Food and Drug Administration (FDA). The University IRB and HRPP apply the principles of the International Conference on Harmonization's Good Clinical Practices (ICH-GCP) to clinical investigations, as adopted by the FDA and insofar as the standards and requirements are consistent with 21 CFR.

The University IRB and HRPP apply the standards of the HIPAA Privacy Rule (45 CFR §160 and Subparts A and E of §164) to research that involves the use of protected health information (PHI).

Additionally, the University IRB and HRPP adhere to the following regulations as applicable to specific research projects:

- Under a Memorandum of Understanding, the University of Utah IRB adheres to the IRB responsibilities and requirements outlined in 38 CFR §16 and the VHA Handbooks when reviewing and making determinations for research conducted at the Veterans Affairs Salt Lake City Health Care System (VASLCHCS).
- Under a Federal-wide Assurance Addendum with the Department of Defense (DoD), the University IRB and HRPP adhere to the requirements outlined in 32 CFR §219, 10 USC §980, and other applicable DoD instructions and research policies when conducting or collaborating in DoD supported human participant research.

The IRB oversees more than 7,000 active human research projects, including clinical trials and related biomedical research, social and behavioral sciences research, and research involving all vulnerable populations described in the Common Rule and related regulatory guidance. The IRB has particular expertise for reviewing molecular and genetic research using biospecimens and data, as well as studies using an exception from informed consent (EFIC).

The University IRB and HRPP have been fully accredited by the Association for Accreditation of Human Research Protection Programs (AAHRPP) since 2007. The FDA has conducted site visits of the IRB in 2004, 2007, 2012, 2017, and 2022. All site visits resulted in no findings for the IRB.

Scientific members of the IRB are practicing physicians, nurses, scientists, and faculty members at the University of Utah, Primary Children's Hospital, and the Salt Lake City Veterans Affairs Medical Center. Non-scientific members include University students, institution staff, and unaffiliated community members.

- Number of IRB members: 121
- Number of IRB staff: 27
- Number of IRB Panels: 9
- Number of Convened Meetings per Month: 12-15

Experience as Single IRB

The University of Utah has been at the forefront of designing and evaluating SIRB methodology through empirical evidence and experience. The University of Utah IRB has served as the SIRB for many multi-center trials, with up to 40 participating sites per trial. The SIRB has supported over 130 multi-center projects, 20 of which are completed and no longer require IRB oversight. The University of Utah has joined the SMART IRB Master Authorization Agreement, allowing for a streamlined SIRB reliance process with the more than 1000 institutions who have also joined. The IRB has an established process for engaging with site investigators and HRPP representatives in order to secure IRB reliance and approval for each participating site.

Use of the University of Utah IRB as a SIRB provides investigators with access to the ERICA Online System, an enhanced electronic system that streamlines submission, review, communication, and documentation for multi-center studies. Access to the ERICA system is available for study personnel at participating sites, including those that are external to the University of Utah. Guest access to studies is also available for study monitors, external auditors, and HRP representatives.

Studies with multiple sites have the option to activate the Site-Control Model on the IRB application, which gives each site autonomy to manage their own IRB documentation, as well as convenient, direct communication with the SIRB. It also allows the lead investigator to delegate regulatory responsibilities across the sites in a more functional way, giving site study teams the ability to help with the submission workload for their site.

Additionally, investigators have access to a comprehensive SIRB consultation process for navigating issues related to study design, methods, and consent documentation for multi-center studies.

Electronic Infrastructure

ERICA is a commercially available software product from Click Commerce, currently owned by Huron Consulting Group. The University has eight-years of experience with this software product and has implemented many customized components that are designed specifically for the needs of the University of Utah HRPP. The University maintains a successful relationship with representatives from Click Commerce and Huron Consulting Group and benefits from the Click Commerce user group meetings and forums that allow for sharing of best practices and customized code as well as providing input for direct improvements to the Click Commerce base product.

ERICA's primary components and functionality include the following:

- IRB Applications

- IRB Project Workspaces and Workflow
- IRB Reviewer Checklists
- IRB Meeting and Agenda Management
- IRB Reviewer Profiles and Training Documentation
- IRB Assessments
- Committees Ancillary to the IRB
- Conflict of Interest Review, Management, and Compliance
- User Roles and Inboxes
- ERICA User Profiles
- ERICA Reports
- Vice President for Research Grant Submissions
- University of Utah Hospitals and Clinics Conflict of Interest Disclosures

ERICA functionality is primarily centered on the IRB application and review process. All IRB submissions, correspondence, and review documentation are completed and maintained electronically. This has greatly benefited the IRB in improving compliance with federal regulation as well as decreasing review times. IRB application and submission types include new applications; amendment applications; continuing review applications; reportable event forms; and site applications for multi-center, single IRB studies.

ERICA also includes many other components for committees ancillary to the IRB, including scientific and safety committees such as radiation safety, institutional biosafety, and oncology protocol review and monitoring; individual and organizational financial conflict of interest; and facilities and resource review committees for Primary Children's Hospital, VASLCHCS Research and Development, and the Resource for Genetic and Epidemiologic Research. ERICA also interfaces with the University's instance of OnCore.

ERICA is managed by the Office of Research Information Systems (ORIS) through the Vice President for Research. ORIS has seven employees, three whose primary responsibility is ERICA development.

Division of Clinical Pharmacology: provides scientific expertise and clinical pharmacology support for clinical trials. The Division specializes in clinical pharmacology support of early-phase studies in adults and children for labeling, a critical element of studies involving investigational or relabeled test products. Table 3 lists trials that have been supported by the Division in Utah and does not include Dr. Watt's prior experience at Duke Clinical Research Institute.

Table 3: Trials supported by clinical pharmacology. NCA - non-compartmental analysis, PopPK - population pharmacokinetic modeling, PBPK - physiologically-based pharmacokinetic modeling.

Trial	Funding	Role	PK Analysis
Amiloride nasal spray PK	Government	PK analysis	NCA
Asthma medication PK in pregnancy	Investigator	PK analysis	PBPK
Atropine gel PK	Foundation	PK analysis	NCA
Citrucline PK in infants	Government	Trial simulation	PopPK
CPCCRN PRECISE Trial	Government	Trial simulation	PopPK
CSF Opportunistic PK	Investigator	PK/PD analysis	PopPK
DICE	Government	PK analysis	PopPK
ECLS Opportunistic PK	Government	PK/PD analysis	PBPK
Hemp extract PK	Industry	PK analysis	NCA
Home collection of breastmilk PK	Government	PK analysis	PBPK
Immunosuppressants bioequivalence	Government	BE analysis	PopPK
IVIG pharmacology	Industry	Safety	PD
LAI bioequivalence	Industry	BE analysis	PopPK
PEAKS	Industry	PK/PD analysis	PopPK
Probiotic efficacy in adolescents	Industry	Efficacy	PD
PTN: CUDDLE	Government	PK/PD analysis	PBPK
PTN: Long Term Antipsychotic Safety	Government	PK analysis	PopPK
PTN Lurasidone PK in children	Government	PK analysis	PopPK
PTN: Ziprasidone PK in children	Government	PK analysis	PopPK

The Division is uniquely positioned to support drug development programs from industry, government, and independent investigators through our longstanding experience in drug development, clinical pharmacology, clinical trial simulation, and PK/PD modeling. The Division comprises 7 faculty (2 MD/PhD pediatricians, 1 MD/PhD adult medicine, 1 MD pediatrician/clinical pharmacologist, 1 PharmD/PhD clinical pharmacologist, and 2 PhD clinical pharmacologists), 5 clinical pharmacology fellows, 1 project leader, 1 research coordinator, and

2 research technicians. Division faculty have expertise in clinical pharmacology across the lifespan from premature neonates through the elderly, including special populations such as pregnancy and renal failure. Division faculty have extensive experience in the regulatory aspects of drug development through past employment and collaborations with the FDA. The Division offers a full portfolio of clinical pharmacology and pharmacometrics services (PK/PD analyses) to meet the needs of investigators who are accessing the TIC. This includes non-compartmental analyses, animal-to-human dose translation, sparse and intense PK sampling analyses, clinical trial simulation, and optimal PK sampling point selection. The Division relies on validated industry and FDA standard software packages for analysis, including Phoenix WinNonLin, NLME, and NONMEM. The Division generates PK reports according to FDA guidance. These PK reports and associated data files (e.g., PK datasets, control files) are provided to the sponsor for regulatory submission if needed.

**JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE
Facilities of Dr. Sapna R. Kudchadkar (Co-Investigator)**

The Johns Hopkins Hospital and Charlotte R. Bloomberg Children's Center: The mission of Johns Hopkins Hospital is to improve the health of the community by setting the standard of excellence in medical education, research, and clinical care. Diverse and inclusive, the Johns Hopkins Hospital educates medical students, scientists, healthcare professionals, and the public; conducts biomedical research; and provides patient-centered medicine to prevent, diagnose, and treat human illness. Specialists in every branch of medical care work collaboratively to foster innovative treatments and accelerate the science of medicine, while preventing and minimizing the public health impact of childhood illness. The 205-bed Charlotte R. Bloomberg Children's Center at Johns Hopkins Hospital, where the 40-bed PICU is located, represents both the birthplace of pediatrics and future of pediatric care. The mission of the Johns Hopkins Children's Center is to provide patient- and family-centered health care in a diverse and inclusive environment, to be a leader in the innovative research that leads to prevention and effective treatment of childhood diseases, and to train the next generation of leaders in pediatric medicine.

Johns Hopkins Pediatric Intensive Care Unit (PICU): The Johns Hopkins PICU is a high-acuity, tertiary unit, and the only neonatal and pediatric ECMO center in the State of Maryland. It is also the only level I pediatric trauma center in Maryland. The PICU is well-experienced in the care of critically ill children with congenital heart disease, and it is a regional heart, kidney, and liver pediatric transplant center. The PICU has been a site for several single-center and multicenter NIH-funded studies including RESTORE, THAPCA, and the ongoing PROSPECT trial. The Johns Hopkins PICU is under the Department of ACCM, and Dr. Kudchadkar oversees the Division of Pediatric Critical Care Medicine in her role as Vice Chair of Pediatric ACCM.

Department of Anesthesiology and Critical Care Medicine (ACCM): The Department of Anesthesiology and Critical Care (ACCM) at Johns Hopkins has demonstrated exceptional commitment to Dr. Kudchadkar as a clinical investigator. The first four years of her academic appointment in ACCM included 75% protected research time through the Johns Hopkins Institutional KL2, which led to her PhD in Clinical Investigation from the Johns Hopkins Bloomberg School of Public Health (JHSPH). JHUSOM and ACCM continued to demonstrate their commitment to Dr. Kudchadkar through a Johns Hopkins Clinician Scientist Award to support her impactful research. The Department of ACCM fully supported Dr. Kudchadkar in the development of the multifaceted PICU Up! intervention, now an NICHD funded clinical trial, which included testing of safety and feasibility in the Johns Hopkins Pediatric Intensive Care Unit (PICU). When Dr. Kudchadkar aimed to characterize acute rehabilitation practices in PICUs in the United States, ACCM funded a Stimulating and Advancing ACCM Research (StAAR) Award, which supported the successful conduct of an 82-site U.S. point prevalence study under her leadership.

Administrative Support: The Department of ACCM provides substantial financial, administrative, and computing support to Dr. Kudchadkar, who is also the Anesthesiologist-in-Chief of the Johns Hopkins Children's Center and Vice Chair for Pediatric ACCM. For instance, Dr. Kudchadkar has access to: (1) highly experienced administrative and sponsored grants specialist staff for the management of all required administrative and grant activities (e.g., NIH financial reporting and progress reports), (2) a high-performance computing cluster with affiliated staff (details below), and (3) funds for travel to professional society meetings and ongoing educational opportunities (e.g., short courses). JHUSOM offers outstanding career enrichment programs (e.g., writing accountability groups and sounding board research meetings). The School also provides extensive support on Institutional Review Board and regulatory processes for research projects.

Office: ACCM and the pediatric divisions provide Dr. Kudchadkar with a private office with appropriate administrative support.

Computer: All study team members in Johns Hopkins Pediatric ACCM have desks with personal computers that are password-protected and registered in the Johns Hopkins Medical Institutions system. The networked computers, a dedicated 4-terabyte laboratory file server, and HP laser printers are available for clinical coordination and data analysis in Dr. Kudchadkar's private office (Bloomberg 6336) and in the clinical research coordinator offices on the same floor. All are equipped with Microsoft Windows 10, Microsoft Office, and several statistical software packages, including SPSS, Stata 15.0, and SAS 9.2. Each is in direct communication with the university's main computer facilities, Welch Medical Library computer facilities, and the internet.

The Secure Analytic Framework Environment (SAFE) is provided to all Johns Hopkins faculty and staff by the Johns Hopkins Institution for Clinical and Translational Research (ICTR). SAFE is a virtual desktop that provides a secure environment to ensure data safety and integrity. The SAFE is installed with productivity software and all statistical software listed above. The SAFE facilitates collaborative data sharing and analysis in a secure environment that complies with federal and JHU requirements to protect patient data and guard against unauthorized access and use.

Storage space for digital research data is provided on an internal, secure, networked research server behind a firewall to ensure data integrity. Files and documents can be accessed on the local network or remotely using a secure VPN (virtual private network) connection.

Dr. Kudchadkar and her research team have unlimited access to comprehensive video- and teleconferencing (Zoom) and shared meeting spaces for technologically supported distance meetings at no cost to the research grant. All computers in the Division of Pediatric ACCM are equipped with this teleconferencing software. It enables multiple users in the same location to have independent access and interaction.

LURIE CHICAGO HOSPITAL Facilities of Dr. Erin Paquette (Co-Investigator)

Scientific Environment:

Ann & Robert H. Lurie Children's Hospital of Chicago

Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's) is one of the premier children's hospitals in the country and the only freestanding hospital in Illinois exclusively for children. The institution has 1,100 pediatric specialists who offer expertise in 70 different specialty areas. Patients come from the greater Chicago metropolitan area, the upper Midwest, and around the nation to access high quality care. With an inpatient capacity of 360 beds, Lurie Children's services include neonatal and pediatric intensive care units, a cardiac intensive care unit and several medical and surgical acute care units. Outpatient facilities include ambulatory surgery, the emergency department, three floors of outpatient clinic facilities, a full-service pediatric radiology department, and pediatric therapy specialists. Lurie Children's has recently expanded into a multi-building campus and the institution provides care at 14 Chicago-area locations. In 2020-2021 Lurie Children's was ranked 12th in the nation by U.S. News and World Report for the provision of pediatric healthcare.

Stanley Manne Children's Research Institute

The Stanley Manne Children's Research Institute (Manne Research Institute) is focused on improving child health, transforming pediatric medicine and ensuring healthier futures through the relentless pursuit of knowledge. All research at Lurie Children's is conducted through Manne Research Institute. In partnership with Northwestern University Feinberg School of Medicine, our scientists work in labs, clinics, at the patient bedside and in the community to unravel the root causes of pediatric and adolescent disease, to understand childhood injury and to find factors that precipitate health problems in childhood and over a lifetime. Established in 1986, Manne Research Institute has more than 400 investigators, 500 staff members, and 100 trainees who contribute to research programs in basic and preclinical sciences, clinical and community trials, population health and outcomes research, and translational medicine. The organizational commitment to research continues to improve our ability to make an impact by supporting innovative studies and includes collaboration with the Northwestern University Clinical and Translational Science Institute (NUCATS). NUCATS, funded through the National Center for Advancing Translational Sciences of the NIH, is the home for clinical and translational science at Northwestern University and its clinical affiliates, including Lurie Children's, Northwestern Memorial Hospital, Northwestern Medical Faculty Foundation, and Shirley Ryan Ability Lab (formerly the Rehabilitation Institute of Chicago). NUCATS provides infrastructure, services, and resources for maximizing and leveraging interdisciplinary "bench to bedside" research. In FY 2020, Lurie Children's grew its overall external support from \$54.2 million in FY19 to \$71.8 million. This 32% increase in external funding is a direct result of Lurie Children's commitment to internally invest in the growth of Lurie Children's research.

Northwestern University

Northwestern University (Northwestern) supports and promotes a vibrant and ever-growing community of clinical and translational scientists that is passionately committed to improving human health. Northwestern was founded in 1851 and is one of the world's premier undergraduate and graduate research universities. It is tied for 9th among US national universities ranked by *U.S. News & World Report* in 2021 and is ranked 24th globally by *Times Higher Education*. Northwestern has notable strengths in medicine, public health, chemistry, nanotechnology, life sciences, engineering, communications, law, journalism, and business/management. Northwestern has more than 50 university research institutes and centers that promote cutting-edge interdisciplinary research. In FY 2020, Northwestern attracted approximately \$887.3 million in sponsored research grant funding. In addition, Northwestern is home to 26 investigators who have been recognized by Clarivate Analytics (formerly the IP and science arm of Thomson Reuters) as Highly Cited Researchers for being among the top 1% of investigators with cited manuscripts in their respective fields; Northwestern ranks 10th worldwide among universities for its number of Highly Cited Researchers. Northwestern is located in Evanston and Chicago, Illinois, and in Doha, Qatar.

Feinberg School of Medicine

The Feinberg School of Medicine (Feinberg) is located on the Chicago campus of Northwestern University. The school is tied for 15th among US medical research schools by *U.S. News & World Report*, and Feinberg research awards totaled \$643 million for FY 2020, of which \$407 million was from NIH. Since FY 2013, NIH funding for Feinberg increased steadily from \$242 million to \$407 million, representing a compound annual growth rate of 7.7%. Since 2008, Feinberg has risen from 27th to 15th among the more than 130 medical schools awarded grants directly from NIH. Industry-sponsored clinical trials in FY 2018 totaled \$62 million. From FY 2012 to FY 2020, participant enrollment in clinical trials more than doubled, from 14,822 to 30,851. Fourteen departments at Feinberg ranked among the top 20 in their specialty discipline in a list of NIH funding to medical schools, ten ranked in the top 10. They are: Public Health (Preventive Medicine and Medical Social Sciences) (1), Physical Medicine and Rehabilitation (1), Obstetrics and Gynecology (2), Physiology (3), Urology (3), Dermatology (5), Neurological Surgery (5), Neurology (6), Pharmacology (7) Anatomy/Cell Biology (10), Microbiology/Immunology (15), Surgery (18), Internal Medicine (19), and Radiation Oncology (20).

Feinberg currently occupies approximately 1.2 million net square feet of space, of which 650,000 net square feet is dedicated to research. Since 2009, Feinberg has invested over \$150,000,000 in renovating almost 400,000 net square feet of owned and leased space. The completed construction includes the Louis A. Simpson & Kimberly K. Querrey Biomedical Research Center in which Lurie Children's Hospital partnered in building 4 floors and where the Stanley Manne Children's Research Institute is housed. Feinberg faculty on all professional tracks number over 1,800.

Northwestern Memorial Healthcare

Northwestern Memorial HealthCare (NMHC) is the corporate parent of 10 hospitals and 5 physician groups comprising over 1500 employed physicians, over 4600 affiliated physicians and 35,000 employees. NMHC has more than 2.6 million outpatient visits across 200+ sites per year. Northwestern Memorial Hospital (NMH), the academic flagship of this system, is one of the country's premier academic hospitals and a national and international referral center. NMH has been recognized again by *U.S. News & World Report* as one of the top "Honor Roll" hospitals--ranked #10 in 2021. NMH has a total of 894 licensed beds and houses the Northwestern University Clinical and Translational Sciences Institute Clinical Research Unit, a developmental therapeutics program, and actively enrolls patients in every clinical department of the hospital. Clinical research studies at NMHC grew from 2,100 in 2010 to 4,445 in FY 2017. The growth of research is one of 3 pillars of the NMHC strategic plan.

Mary Ann & J. Milburn Smith Child Health Outcomes, Research, and Evaluation Center

The mission of the Smith Child Health Outcomes, Research, and Evaluation Center (Smith Child Health Center) is to advance innovative research to improve the well-being, health, and healthcare of diverse populations of children. The vision of the Smith Child Health Center is to become the premiere destination for population health, health services, social and behavioral researchers who focus on children and youth.

The Smith Child Health Center has 17 research labs/programs and is also home to the Catalyst, a "hub" of qualitative and quantitative expertise and resources in pediatric population health, health services research, and evaluation. Together, the Center is the research home for 21 faculty members (physician-investigators and research investigators) and over 20 research staff, many of whom have master's-level training in public health

and epidemiology. The multidisciplinary research teams and the Catalyst strengthen interdisciplinary collaboration, academic competitiveness and capacity within population health and health services research for Lurie Children's Hospital. Investigators' work is funded by a wide variety of federal, foundation, and philanthropic sources. The Center's deliberately innovative, rigorously evaluated initiatives have been published in leading peer-reviewed journals of medical care, public health, and health policy.

The Smith Child Health Center is located at 680 N. Lakeshore Drive on the Feinberg campus in Chicago, where investigators and staff have approximately 8,262 square feet of office space. All personnel have their own standard-sized office with office equipment. The Smith Child Health Center is equipped with multiple locked storage rooms (for confidential files), unlocked storage rooms (for general storage), and 3 video conference enabled conference rooms, each with Polycom 7000 units and plasma screens. Investigators also have access to additional facilities at Lurie Children's main Hospital and the Stanley Manne Research Institute in the Louis A. Simpson & Kimberly K. Querrey Biomedical Research Center building, both just a short walk away.

Patrick M. Magoon Institute for Healthy Communities

Launched in 2020 and building on decades of community health work, the Patrick M. Magoon Institute for Healthy Communities (Magoon Institute) at Lurie Children's (based in 680 N Lakeshore Drive on the Feinberg campus in Chicago) is designed to maximize the positive impact Lurie Children's and its partners have on child and adolescent health and wellness in the community. The Magoon Institute serves as the hub for all community-focused initiatives at Lurie Children's, expanding the efforts of the Healthy Communities program that was established in 2017. This department aligns clinical, research, education and advocacy expertise with community health, outreach, and engagement initiatives. The Magoon Institute, with its five Programs and dozens of initiatives, leads the development and implementation of Lurie Children's Community Health Needs Assessment and Implementation Strategy, builds strong collaborations with community organizations, facilitates community-engaged outreach and research initiatives to advance and implement evidence-informed child and adolescent health programs and practices, and partners with leaders across the organization to work towards an overall goal of advancing health equity for youth and their families across Chicago.

Office: All study investigators have private offices with private phone, shared fax, administrative support, and dedicated desktops or laptops running current versions of Microsoft Office. All computers have high- speed internet connections behind secured, hospital firewalls and access to color and/or B&W laser printers.

PARTICIPATING CLINICAL SITES Facilities from 14 clinical sites are listed below:

(1) ARKANSAS CHILDREN'S HOSPITAL

Scientific Environment:

Arkansas Children's, Inc. is the only healthcare system in the state solely dedicated to caring for Arkansas' more than 700,000 children. The private, non-profit organization includes two pediatric hospitals, a pediatric research institute and USDA nutrition center, a philanthropic foundation, regional alliances and clinics, and telemedicine and statewide outreach programs—all focused on fulfilling a promise to define and deliver unprecedented child health. Generous philanthropic and volunteer engagement has sustained Arkansas Children's since it began as an orphanage in 1912 and today ensures the state's only pediatric health system can deliver on its promise of unprecedented child health.

The Arkansas Children's Research Institute (ACRI) is a not-for-profit corporation owned by Arkansas Children's, Inc. ACRI is located in Little Rock on the campus of Arkansas Children's Hospital (ACH). ACRI was established to provide an on-site research environment for UAMS faculty and scientists. ACRI officially opened on the ACH campus in 1992. Today, led by Peter Mourani, MD as its President, ACRI has over 120 pediatric researchers with expertise and experience that span the breadth of medical disciplines. ACRI's roster of investigators works to fulfill its mission to improve children's health, development, and well-being through high quality research. In fiscal year 2022, ACRI researchers received \$34.5 million in grants and contracts from federal, state, and private agencies, industry sponsors, and philanthropic donations. Over \$16.1 million was from the National Institutes of Health.

Currently, ACRI has over 196,000 ft² of research space. The four-story Research Institute Building is the central location of ACRI administrative offices and houses researcher offices, conference space, laboratories, and ACRI's animal facility. The two-story Arkansas Children's Nutrition Center (ACNC) adjoins to the south of the

Research Building. Opened in 1997, the ACNC houses one of six United States Department of Agriculture-Agricultural Research Service (USDA-ARS) National Human Nutrition Centers.

Remaining ACRI research space includes the Pediatric Clinical Research Unit located in the main ACH hospital building two blocks north of the Research Institute Building. In addition, ACRI maintains the Research Pharmacy in the hospital. ACH also affords clinic and unit space for investigators performing their research at the main hospital building. ACRI researchers also have assigned, dedicated office, clinic, and laboratory space on the ACH campus in the Sturgis Building (adjoining the main hospital building and one block north of the research building), Professional Building 2 (adjoining the research building to the east), and the Dennis Developmental Center (one block south of the research building).

Research Operations Support Staff: ACRI offers a staff of qualified regulatory specialist, budget specialist, clinical research coordinators (CRCs) and research nurses to assist investigators with feasibility assessments, budget development, pre-site visits, IRB submissions, day-to-day operations of their clinical studies, audit support, and study close-out. The costs associated with these services are direct expenses to the specific clinical study and are paid for by the sponsor, while the training and education effort of staff members is provided by the ACRI. Operations support personnel are organized into thematically/specialty oriented teams (e.g. PICU, Neonatology, Allergy, Hematology, Oncology, etc.). Each team includes a CRC supervisor and CRCs linked to a dedicated regulatory, and budget specialists. The teams are then supervised by the Clinical Research Operations Manager and Director.

Pediatric Clinical Research Unit: ACRI researchers have been involved in pediatric clinical trials for over 30 years. These clinical studies assure medicines, vaccines, and treatments for children are safe and effective. The majority of these studies are industry sponsored, while federal agency (FDA and NIH) and other grant awards supported the remaining trials. Many researchers conduct their clinical trials at ACRI's Pediatric Clinical Research Unit (PCRU) located at ACH's main hospital building on the 2nd floor and easily accessible to all inpatient units and most outpatient clinics. Available 24 hours a day, 7 days a week, the PCRU provides a 4,000-ft² facility for high-quality clinical pediatric research. The PCRU has 4 semi-private and 2 private beds as well as a full laboratory available to all research teams, including centrifuges, heating baths and blocks, homogenizer, work bench space, and two freezers (-20°C and -70°C) for sample processing. It also includes a kitchen, offices, equipment and protocol supply storage, waiting area, and small conference room. The PCRU is staffed by a team of research nurses that provide the full range of nursing support activities required by research protocols. ACRI provides an adjacent on-site Research Pharmacy for the PCRU and hospital on an adjoining corridor.

Research Pharmacy: ACRI maintains a 1,035-ft² Research Pharmacy at ACH in support of inpatient and outpatient trials by ACRI researchers. Its staff of research pharmacists is accountable for drugs administered from the initiation through the completion of clinical trials at Arkansas Children's. They oversee the formulating, dispensing, accounting, blinding, and storing of the drugs and the documentation of these activities. Research Pharmacy staff also provide input on study design and planning. The Research Pharmacy has secure access and segregated storage space for drugs that require ambient temperature, refrigeration, or -20°C or -80°C storage. The Research Pharmacists also have access to laminar flow hoods as well as a dedicated viral vector hood.

Laboratory and Specimen Processing: In addition to the research laboratory contained in the PCRU, there is dedicated laboratory processing space with the ACH laboratory on the 2nd floor which is easily accessible from all inpatient units (including the PICU) and most outpatient clinics. The laboratory, available to all research teams, includes a class II biosafety hood, centrifuges, heating baths and blocks, homogenizer, work bench space, a refrigerator, two freezers (-20°C and -70°C) for sample processing, and access to dry ice for specimen shipping.

University of Arkansas for Medical Sciences:

The University of Arkansas for Medical Sciences (UAMS) provides the only medical and pharmaceutical education in Arkansas. UAMS serves a predominately rural state, with a diverse population of over 2.8 million persons (75.9% Caucasian/non-Hispanic, 15.4% African-American/non-Hispanic, 5.3% Hispanic/Latino, 0.6% Native American, and 1.2% Asian/Pacific Islander). Located less than two miles from the ACH campus, it is the state's largest, most comprehensive facility for medical treatment and biomedical research. UAMS is the state's largest basic and applied research institution, with more than \$111 million in annual research funding, grants and contracts and internationally renowned programs in multiple myeloma, aging, cancer and other areas. The Colleges of Medicine, Nursing, Pharmacy, Public Health, and Health Related Professions as well as the Graduate School and regional programs are located at UAMS. UAMS employs more than 5,000 health

professionals and graduates nearly 600 MDs, PhDs, nurses, pharmacists, and allied health professionals each year.

Department of Pediatrics (College of Medicine): The Department of Pediatrics is the largest department of UAMS College of Medicine in Little Rock, Arkansas. The main offices of the Department are located on the campus of Arkansas Children's Hospital, a long-time clinical and teaching affiliate of UAMS. The two institutions coordinate clinical service, educational programs and research initiatives among pediatrics faculty and other university faculty. Pediatrics faculty are also assigned to selected areas within University Hospital and physicians from the department provide clinical services on a regular basis to regional clinics around the state. Pediatrics staffing totals more than 1,000 employees, including more than 190 faculty members and 950 professionals, paraprofessionals, and support staff, working in 28 sections in the department.

Fay W. Boozman College of Public Health: The UAMS College of Public Health was established in 2001 and renamed in 2005. COPH has rapidly established a broad complement of teaching programs and is beginning to develop its research and service activities directed toward meeting its mission of improving the health and promoting the well-being of individuals, families, and communities in Arkansas. Working in collaboration with the other academic units at UAMS (the Colleges of Medicine, Nursing, Pharmacy, and Health Related Professions as well as the Graduate School), the new COPH brings a different perspective to UAMS's traditional medical care services. COPH's primary focus is on a population or community-wide perspective, rather than a focus on medical care for an individual. COPH has a strong emphasis on health promotion and primary prevention as a cost-effective way to achieve general health and well-being for all Arkansans. It also has a fundamental commitment to policy development and information-gathering necessary to develop sound policy, since good health is ultimately a reflection of an optimally functioning health care system.

COPH offers the following programs: 1) baccalaureate certificates in Public Health, Environmental and Occupational Health, and Regulatory Science; 2) Master's degrees in Public Health, Health Service Administration, and Occupational and Environmental Health; and 3) Doctoral degrees of Public Health Leadership, Health Systems Research and Health Promotion and Prevention Research, and Epidemiology. Combined degree programs are also available with medical, juris, and pharmacology doctoral programs as well as graduate programs in public service and communication science. COPH has three centers dedicated to research in the areas of community-participatory, health disparities, and obesity research. Active research from COPH faculty includes cancer control, diabetes, environmental/occupational health, health disparities, health systems, heart disease, long-term care, obesity, tobacco, and stroke.

Biostatistics Core: Through its Biostatistics Core, ACRI with support from Arkansas Children's provides its clinical and biomedical researchers access to statistical and database support. The mission of the Biostatistics Core is to provide outstanding statistical and database support to clinical, applied, translational, and biomedical researchers while advancing the reputation and research capacity of ACRI and ACH. Developing long-term, collaborative researchers is the key to achieve our mission. These services are not directly utilized for this proposal but may serve as back-up if any issues arise.

Genomics Resource: The ACRI Genomics Resource supports genomics research for the Center for Translational Pediatric Research (CTPR) COBRE grant [P20GM121293; see "Centers of Biomedical Research Excellence (COBRE) at ACRI" below] as well as for researchers on the ACH campus. The genomics team has substantial technical and practical experience in high-throughput sequencing. The resource has made major investments in state-of-the-art instrumentation and has recruited experienced staff to manage it. The Genomics Resource provides researchers with initial consultation for study design and support. These services are not directly utilized for this proposal but may serve as back-up if any issues arise.

Metabolomics Core: With a 2,200 square-foot laboratory dedicated to the chemical analysis of biological samples and diets, the Arkansas Children's Nutrition Center Metabolomics and Analytical Chemistry Core, directed by Colin Kay, Ph.D. (Scientific Director) and Renny Lan, Ph.D. (Operations Director), as well as a full-time chemist and several affiliated post-doctoral trainees responsible for operation and maintenance the LC-MS systems, and work closely with the Arkansas Children's Nutrition Center Biostatistics and Data Innovation Core to analyze and process metabolomic, lipidomic, and targeted assay data (targeted and untargeted) from a variety of human and animal samples including plasma, serum, lung fluid, tissues, urine, milk, and fecal/intestinal contents. These services are not directly utilized for this proposal but may serve as back-up if any need arise.

Clinical Environment:

Arkansas Children's Hospital: Arkansas Children's Hospital (ACH), established in 1912, is a 336-bed, private, non-profit hospital with an active medical staff of more than 500. ACH is the state's leading health care facility dedicated exclusively to children and one of the largest pediatric hospitals in the nation. Located in Little Rock in the center of the state, it serves a population base of approximately 5 million people in Arkansas and surrounding states. ACH is a teaching hospital of the University of Arkansas for Medical Sciences (UAMS), the only medical school and health sciences university in Arkansas. Essentially, all physicians and scientists on the ACH campus are UAMS faculty. **ACH is a Magnet-recognized facility operating the state's only Level I pediatric trauma center, the state's only burn center, the state's only Level IV neonatal intensive care unit, the state's only pediatric intensive care unit, the state's only pediatric surgery program with Level 1 verification from the American College of Surgeons, the state's only magnetoencephalography (MEG) system for neurosurgical planning and cutting-edge research, and the state's only nationally recognized pediatric transport program.** Additionally, ACH is nationally ranked by U.S. News & World Report in four pediatric subspecialties (2020-2021): Cardiology & Heart Surgery, Nephrology, Pulmonology, and Urology. ACH is one of only five hospitals in the nation that have achieved Magnet Status, ACS Level 1 verification, and a Beacon Award from the American Association of Critical-Care Nurses. ACH is dedicated to offering medical services to all children regardless of their race, ethnicity, religion, national origin, gender, or ability to pay.

The ACH campus covers 32 city blocks over 64 acres with a floor space totaling over 2,050,000 ft². Inpatient specialty units include cardiovascular, newborn, and pediatric intensive care units; orthopedics; hematology/oncology; renal dialysis; extracorporeal membrane oxygenation; and many others. During fiscal year 2022, 319,416 visits were made by patients to the 100+ general and pediatric specialty clinics and the emergency room at ACH. Males and females represented approximately 49.0% and 47.4%, respectively (3.6% not specified), of the total patient population. In fiscal year 2022, Hispanics represented 11.1% of the total patient population. African Americans and Caucasians comprised approximately 31.8% and 41.3% of the total patient population, respectively. Native Americans and Asians represented approximately 0.2% and 0.8% of the patients seen annually, respectively.

The Pediatric Intensive Care Unit (PICU) at Arkansas Children's Hospital is a 26 bed unit that has a median admits 1560 per year. The PICU is located on the 3rd floor of the hospital and readily accessible from all inpatient units and the Pediatric Clinical Research Unit (PCRU). The PICU is staffed entirely by University of Arkansas for Medical Sciences faculty in the Sections of Critical Care Medicine in the Department of Pediatrics. There is a total of 21 attending physicians, all of whom are American Board of Pediatrics board certified/eligible in pediatric critical care. Several attending physicians also attend to the Pediatric Sedation service and/or the Pediatric Cardiovascular Intensive Care unit. The section also has 3 dual trained surgery-critical care attending physicians. There are 5 advanced nurse practitioners. The section has a ACGME fellowship program (the largest at ACH) with a total of 6 fellows. Leadership includes a Section Chief, Medical Director, Research Director, Quality Improvement Director, Safety Director, Fellowship/Education Director, Advance Practice Provider Director, Nurse Manager, Respiratory Therapy Manager, and Business Manager. This team meets monthly to manage priorities and operational issues of the PICU.

The Section of Critical Care has 3 experienced full time clinical research coordinators (CRCs) and is actively recruiting for a fourth, who provide 24/7 screening and enrollment capabilities. The CRCs are hired and managed centrally by the Arkansas Children's Research Institute (ACRI; see section below), but are fully dedicated to PICU research. The CRCs in conjunction with the Section Research Director (Ron Sanders, MD; co-investigator on this application) screen for all studies and apply a priori developed algorithms to determine which patients to approach for each study, maximizing the possibility for co-enrollment if study protocols allow. The majority of attending physicians in the Section participate as a site PI on multi-center studies, and the PICU has a strong culture of research ensuring extremely strong enrollment proportions. An active research pharmacy also provides 7 day a week coverage for drug related studies and trials. We have been active members as either a primary or ancillary site for NICHD Collaborative Pediatric Critical Care Research group since 2006, and currently enroll (3rd of 25 sites opened) in the CPCCRN PeRsonalizEd immunomodulation in pediatriC sepsIS-inducEd MODS (PRECISE) trial. We are also a site member of the Pediatric Acute Lung Injury and Sepsis Investigators network since 2009. We have screened, enrolled, and collected data for some of the most important pediatric critical care clinical studies in the field, such as, THAPCA, H1N1 Influenza pandemic, CRISIS, NEAR4KIDS, PROSPECT, LEOPARDS and the PRECISE trial. We currently have over 25 active clinical studies operating in the PICU. ACH serves as a teaching hospital for UAMS, the only medical school and health sciences university in Arkansas, and is home to the UAMS Department of Pediatrics. Medical students, residents, and other health-related professionals receive their primary pediatric training at ACH. UAMS faculty composes most of the over 500 physicians on the ACH staff.

Arkansas Children's Northwest: Opened in 2018, Arkansas Children's Northwest (ACNW) is the first and only pediatric hospital in the Northwest Arkansas region. It is a Level IV pediatric trauma center. Located in Springdale, ACNW operates a 24-bed inpatient unit, a surgical unit with five operating rooms, outpatient clinics offering over 20 subspecialties, diagnostic services, imaging capabilities, occupational therapy services, and Northwest Arkansas' only pediatric emergency department, equipped with 30 exam rooms. Notably, this hospital lacks a PICU, and transports 100% of its critically ill patients to the ACH PICU.

Administrative Support: ACRI's research support staff acts as facilitators to ease the administrative burden of sponsored research. At the same time, the staff provides an array of unique services outside the general area of research administration.

The administrative staff supports ACRI faculty throughout the grant process, providing pre- and post-award assistance. These services include proposal development assistance, acting as liaison between the researcher and the sponsoring agency while ensuring the research complies with the agency guidelines and administrative requirements, assisting with the preparation of appropriate internal and external application forms, auditing of studies to ensure compliance with federal guidelines, and determining the accuracy of proposal budgets.

Security: ACH appropriately staffs a Security department for the hospital campus including ACRI. Uniformed officers station a post as well as provide outside patrols for ACRI. Further security measures at all entry points include monitored cameras and card readers. Security maintains camera recordings and card entries. Additional monitored cameras and card readers are located at key locations throughout ACRI. ACH's Building Automation department continually monitors security, fire, and equipment alarms for ACRI. Upon an alarm, Building Automation immediately notifies appropriate ACH and ACRI personnel. ACRI has building-wide intercom systems to notify personnel during emergencies.

(2) CHILDREN'S NATIONAL MEDICAL CENTER

Children's National Hospital (CNH)

Children's National Hospital (CNH) is the only exclusive provider of pediatric care in the Washington, DC metropolitan area, and is the only freestanding children's hospital between the city of (i) Philadelphia to the North,(ii) Pittsburgh to the West and (iii) Norfolk to the South. Serving the nation for 150 years, CNH is a proven leader in the development and application of innovative new treatments for childhood illness and injury and ranks consistently among the best pediatric hospitals in America by the U.S. News and World Report. Since 2017, CNH has ranked within the top 10 children's hospitals in this comprehensive survey, with a ranking of 7th overall in the most recent survey. This impressive overall ranking strongly argues for the high-quality of care for children with critical illnesses in our health system.

CNH has an internationally recognized team of pediatric healthcare professionals that care for patients from throughout the region, nation and world, with more than 450,000 outpatient visits, 15,000 inpatient admissions, 100,000 emergency department visits and 4000 pediatric intensive care unit admissions annually. CNH consists of a 335-bed in-patient facility with 144 critical care beds (48 in Pediatric Intensive Care Unit, 26 in Cardiac Intensive Care Unit and 70 in the Neonatal Intensive Care Unit) with a planned expansion of an additional 18 PICU beds in fall of 2020. In addition, 5 community-based health centers in the District of Columbia, and 7 regional outpatient facilities in Maryland and Virginia are a part of the CNH system of care that serves as the regional referral center for general pediatrics and the specialties of pediatric emergency, trauma, and critical care. As the largest non-governmental provider of pediatric care in the District of Columbia, CNH provides more than \$50 million in uncompensated care. CNH is staffed by more than 900 physicians in the Children's National Health Care Network and more than 700 full-time faculty members (both clinical and nonclinical) with academic appointments at The George Washington University (GWU) School of Medicine and Health Sciences.

Resources contributing to the success of the CPCCRN at CNH

For this application, all of the facilities and resources are already in place at CNH to successfully complete this application. First, sufficient work space and computer access for research coordinators ($n = 5$ currently employed by the Division of Critical Care Medicine and available for this work and other funded projects) is located on the 5th Floor of the Main Hospital. Second, bench laboratory space within the Center for Genetic Medicine (see Table 1 below for outline of Research Institutes within Children's National Research and Innovation Institutes) is available to process samples including but not limited to centrifuging blood, preparing samples for processing, measuring/mixing reagents with biological specimens, performing preliminary processing and shipping to central

laboratory for assessment. This infrastructure has been used over the past 5 years for CPCCRN projects that compromise the preliminary data for this application. Third, 5 research pharmacists work at CNH to assist with dispensing of medications for clinical studies. Again, this group has been actively working with the preliminary projects described in the overall application. Fourth, CNH, CNRI and the Division of CCM have a close relationship with the Information Technology infrastructure. As described in the body of this site application, the Bear Institute is a CNH-based collaboration with CERNER to link clinical and research applications with the electronic health record. This collaboration has successfully led to Dr. Pollack's group continuing to develop EHR-based outcomes and Dr. Anita Patel's successful K12 application. Fifth, since CNH has been well-integrated into the current CPCCRN network, we have an existing agreement with the SMART IRB with the University of Utah to expedite the single IRB for this application. Moreover, we have existing Material Transfer Agreements with Ohio State University that will be necessary for Aim 3 of this application. Lastly, CNH is the only free-standing children's hospital that is a lead institution for a Clinical Translational Science Award (at CNH, named CTSI-CN, see Table 1). As a lead institution, we have access to many core facilities and resources within this infrastructure grant. These will be of great assistance for Aim 3 of this application and any other potential grants that might be operationalized within CPCCRN.

Table 1. Children's Research Institute Organizational Structure**Children's Research Institute (CNRI)**

Center for Cancer and Immunology Research	Programs: Research and affiliated clinical faculty with interests spanning T cell biology, inflammation, cancer immunology, transplantation and autoimmune diseases. Space/Equipment: 15,000 sq. ft. of web lab space. Shared equipment includes 8-color flow cytometer, flow-based cell-sorter, AUTOMACS magnetic bead-based cell sorter (Miltenyi Biotech), and Luminex machine. Dedicated space for HIV research containing all necessary equipment for cell culture.
Center for Genetic Medicine Research	Programs: Houses Department of Integrative Systems Biology (ISB), the graduate program in biochemistry and systems biology at GW's School of Medicine and Health Sciences. Students pursue dissertation research in laboratories at CNH, GW, and NIH while completing course requirements, such as Molecular Bases of Human Diseases, Genes to Cells, Advanced Proteomic Methods, Integrative Bioinformatics, and Applied Biostatistics. Space: 18,000 sq. ft. in an open laboratory infrastructure. Emphasis on translational research and emerging technologies (e.g., genomics, proteomics, and large-scale public access databases).
Center for Neuroscience Research	Programs: Lab-based developmental neuroscientists and clinical investigators neural stem cells and developmental neurobiology, brain injury and brain protection, perinatal hypoxia and hyperoxia, epilepsy, neuro-oncology, neurofibromatosis, attention deficit hyperactivity disorder, and autism. Space/Infrastructure: 12,000 sq. ft. of open lab space and support rooms.
Center for Translational Science	Program: Spans the full translational continuum from T0 research (preclinical) to T1 research (bench-to-bedside) to T2 research (evidence-based guidelines) to T3 research (implementation science) to T4 research (community-based research and health policy). Three major research sub-themes: 1) molecular pathogenesis and experimental therapeutics; 2) patient-oriented research (reducing symptoms and preventing complications of illnesses); and 3) behavioral and community research (pediatric health services and health disparities). Includes investigator- initiated programs and NIH-funded consortia.
Sheikh Zayed Institute for Pediatric Surgical Innovation (SZIPSI)	Program: Founded in 2010 through a \$150 million gift from the government of Abu Dhabi with the mission of making pediatric surgery more precise, less invasive, and pain free. Space: 22,000 sq. ft. of laboratory and office space to facilitate current and future research collaborations. Equipment: Objet Connex 500 rapid prototyping systems for producing parts and anatomical models; 10 workstations with network access to SolidWorks design software; VisionSense 4 mm laparoscopic 3D video system with 0° and 30° scopes; BK laparoscopic ultrasound with 4-way flex movement; 3 Kuka lightweight robots for research in medical robotics; High Intensity focused ultrasound (HIFU) research equipment; ENVISIONTEC 3D tissue printer; DaVinci surgical robot testbed with open source interface.

Clinical and Translational Science Institute at CNH (CTSI-CN)	<p>Program: NIH-funded CTSA collaboration between CNH and GWU. Highly integrated, cost-effective, investigator-focused resources designed to overcome research barriers, promote collaborative research, and provide research training with a special focus on children's health. Pediatric research strengths in rare diseases, asthma, and neuro-developmental disabilities. Collaborates with national network of 1,200 community health centers. Emphasis on health disparities and childhood antecedents to adult diseases.</p> <p>Infrastructure: Clinical studies resource, biomedical informatics, REDCap, clinical data warehouse, biostatistics and research design, regulatory support</p> <p>Education/career development: MS and graduate certificate in Clinical and Translational Research, component certificates, K scholars, mentor program, learning management system</p> <p>Team science and innovation: CTSAs, industry/biotechnology, patient organizations, pilot awards, vouchers, Open Studios, genomics, proteomics, imaging, Grants Enhancement Program (supports junior faculty writing/implementing career development awards, monitors progress of early-stage investigators, provides review/critique from senior investigators for R-level NIH grant applications)</p> <p>Community and population resources: Community-oriented research, population/public health research, Science Care, community-based organizations.</p>
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(3) CHILDREN'S HOSPITAL OF MICHIGAN

Scientific Environment:

The facilities and other resources available to Dr. Meert at Children's Hospital of Michigan (CHM) include everything necessary for her and her research team to participate fully and to successfully complete the research described in this application. Dr. Meert has access to the clinical resources of the Detroit Medical Center (DMC), the Children's Hospital of Michigan (CHM), and the CHM Pediatric and Cardiac Intensive Care Units (PICU & CICU) from which research participants may be recruited. Dr. Meert and her research team have sufficient office space, conference rooms, computers and information technology support, and clinical and research laboratory support for designing and conducting research, analyzing data, and preparing manuscripts. Other important facilities and resources include the Central Michigan University (CMU) Clinical Research Institute (CRI) located at Children's Hospital of Michigan providing grants management and administrative support, the Clinical Research Center, and intellectual resources available through other investigators and networks active at CHM.

Research Laboratory: Please see CMU Clinical Research Institute (CRI), below. The CRI has 6,895 square feet of wet bench laboratory space within CHM for use by clinical researchers. The laboratory is designed around the concept of an open laboratory model to encourage interactions between investigators. All equipment needed at the local site for participation in the proposed research is available to Dr. Meert and her research team.

Clinical Laboratories: The DMC University Laboratories is a regional, integrated clinical laboratory system providing services to all DMC hospitals including CHM. In addition, DMC University Laboratories operates a full service commercial outreach program that includes patient service centers, remote ambulatory laboratories, marketing staff, courier system and billing department. DMC University Laboratories are comprised of a Core Laboratory and Specialty Laboratories that provide a full range of routine and special diagnostic services 24 hours per day, 7 days per week. The Core Laboratory is comprised of Processing, Microbiology, Hematology, Hematopathology, Coagulation, Flow Cytometry, Molecular Microbiology, Virology, Chemistry, Special Chemistry and Toxicology. The Specialty Laboratories are comprised of Molecular Genetics, Cytogenetics, Biochemical Genetics, HLA-Immunogenetics, Histology, Immunohistochemistry, Blood Bank, Cytology and Pathology. A menu of over 1,000 laboratory tests has resulted in less than 1% of tests sent to outside reference laboratories. DMC University Laboratories provides reference laboratory services to many other healthcare systems in southeast Michigan. DMC University Laboratories is fully licensed and provides services at discount rates for clinical research protocols.

Clinical Environment:

Detroit Medical Center (DMC): The DMC is the leading academically integrated healthcare system in metropolitan Detroit and the largest healthcare provider in southeast Michigan. The DMC has a combined total of over 2,000 licensed beds, making it one of the largest multi-hospital complexes in the U.S. Care is provided at the DMC by over 3,000 affiliated physicians and 12,000 employees. The DMC currently sponsors more than

100 residency and fellowship programs, training over 1,000 physicians each year. The DMC trains the majority of practicing physicians in the State of Michigan including 70 percent of the state's trauma surgeons and 60 percent of its emergency physicians. The DMC's Central Campus is located over 110 acres in north-central Detroit. The DMC Central Campus includes Children's Hospital of Michigan, Detroit Receiving Hospital, Harper University Hospital, DMC Heart Hospital, Hutzel Women's Hospital, and the Rehabilitation Institute of Michigan. Also located on the central campus and partnering with the DMC are the Kresge Eye Institute and the Karmanos Cancer Institute. The DMC also operates Sinai-Grace Hospital, Huron Valley Hospital and the DMC Surgery Hospital in the Detroit metropolitan area.

Children's Hospital of Michigan (CHM): The CHM is a freestanding children's hospital that provides care for children from Michigan, the U.S. and several other countries in more than 40 pediatric specialties. CHM has 228 inpatient beds. Each year, CHM admits over 13,000 children to its inpatient services and has over 125,000 outpatient visits in its ambulatory clinics. The CHM Emergency Department is one of the busiest in the U.S. with 95,000 visits annually. CHM is an American College of Surgeons accredited Level 1 Pediatric Trauma Center and Michigan's only American Burn Association verified Pediatric Burn Center. The Burn Center is one of a few pediatric centers in the US to achieve this verification. CHM is ranked nationally (US News & World Report) in 4 pediatric specialties. CHM's PANDA-One Transport Team is the state's only dedicated pediatric and neonatal transport team. PANDA-One uses dedicated ground ambulances, and air ambulances via helicopter and fixed wing aircraft to transport more than 1,200 neonatal and pediatric patients from hospitals throughout Michigan, surrounding states and Ontario, Canada to its Detroit location. In 2017, CHM opened a new 6-story, 248,000 square foot, \$155 million tower continuous with the old hospital that includes a new ground level Emergency Department (ED), expanded Neonatal (NICU), Pediatric (PICU) and Cardiac (CICU) intensive care units with private rooms, a new Radiology Department, and updated Surgery Department including new operating rooms, and pre- and post-operative care areas. The new PICU and CICU has 48 beds (34 dedicated to general medical/surgical patients and 14 dedicated to cardiovascular patients), and new NICU has 39 beds. The New ED has 52 treatment rooms, 4 trauma bays and 6 behavioral health rooms. The CHM Specialty Center which opened in 2013 is located across the street from the hospital and provides outpatient care, research and education for children and their families. Child Health Advocacy Programs at CHM include the Helppie Institute for Child Health Advocacy, Kohl's Trauma Related Injury Prevention Program, Child Protection Center and Palliative Care Services. The CHM staff is comprised of more than 200 pediatricians, 125 pediatric specialists, 100 residents and fellows, 600 pediatric nurses and over 1000 employees with a special understanding of children's needs.

Pediatric and Cardiac Intensive Care Units at CHM: The PICU and CICU at CHM are housed in the new (2017) CHM tower described above. These ICUs have a total of 48 beds, each in private rooms. Fourteen of the 48-beds are dedicated to cardiac/cardiovascular surgery patients, and the rest comprise a general multidisciplinary medical/surgical unit. The PICU/CICU admits approximately 2,000 medical and surgical patients annually. Both the PICU and CICU are administratively managed and staffed by attending physicians and fellows in the Division of Pediatric Critical Care Medicine. The pediatric intensivists are the primary attendings for all medical patients and co-manage all surgical patients with the relevant surgical subspecialty service. The Division of Pediatric Critical Care Medicine has 15 attending pediatric intensivists; all of whom are American Board of Pediatrics (ABP) certified or eligible in Pediatric Critical Care Medicine. The Pediatric Critical Care Medicine fellowship program has a total of 9 fellows. Procedures routinely performed in the PICU/CICU include endotracheal intubation, conventional and high frequency mechanical ventilation (oscillator and jet), central and arterial line placement, bronchoscopy, continuous renal replacement therapy, and ECLS. Each bed is equipped for advanced hemodynamic, respiratory and neurologic monitoring (General Electric) and includes telemetry, six central monitoring stations and one satellite station. Vital signs, intake and output, and fluid and medication administration are recorded hourly. Two College of American Pathologist accredited blood gas laboratories complete with blood gas analyzers that perform oximetry and electrolyte analysis are located within the PICU/CICU. Forty desktop computers are located at central work stations, 24 desktop computers are located between patient rooms, 38 roving computers with scanners are available for use at the bedside, and eight roving laptop computers are available for physician use. All computers provide immediate access to the DMC-wide Clinical Information System (CIS). CIS is an electronic medical record that includes all charting information from physicians, nursing and respiratory therapists, orders and reports. Office space for nursing administrative staff is located on the unit. On-call rooms for PICU attending staff, fellows, and residents are also located on the unit.

Pediatric Trauma Center: CHM is the first American College of Surgeons (ACS) verified, free-standing Level 1 Pediatric Trauma Center in Michigan. ACS verification confirms the CHM Pediatric Trauma Center is committed

to the highest quality trauma care for all injured patients. The Trauma Center provides care to injured children and their families from the time of injury through rehabilitation and recovery. Emergency transport for pediatric trauma patients is provided by PANDA One, Michigan's only dedicated pediatric and neonatal ambulance service and transport team. Trauma patients are cared for in the Emergency Department, PICU, Burn Unit, and surgical ward, as needed, and have available 24-hour emergency CT scans, angiographies and other diagnostic procedures. Additionally, an operating room is reserved for trauma patients 24 hours a day. The Trauma Center is a member of the State of Michigan Region 2 South State Trauma System, Regional Disaster Network and Detroit East Medical Control Authority. It also provides leadership in community-based injury prevention and pediatric continuing education for healthcare professionals throughout southeast Michigan. The staff conducts, evaluates and disseminates evidence based research and outcomes regionally, nationally and internationally.

Investigational Drug Services (IDS): The Dept. of Pharmaceutical Services at CHM maintains an Investigational Drug Service (IDS) that is responsible for all investigational drugs dispensed and administered throughout the hospital. The IDS is staffed by one full time research pharmacist, three back up pharmacists and a pharmacy technician and is available 24 hours per day, 7 days per week. The IDS has been in operation since 1985. In any given year, the IDS coordinates, monitors, and dispenses study medications for 40-50 ongoing studies. These include NIH sponsored studies, Children's Oncology Group studies, drug manufacturer sponsored studies and CHM investigator-initiated studies. The IDS has experience as the primary pharmacy site coordinator for multi-center studies. The IDS provides the following services to investigators: study protocol review; identification of pharmacy-related issues; advising on study drug administration methods and processes; dispensing process development; pharmacy and healthcare provider in-services; maintaining study files such as IRB approvals, protocol amendments, drug accountability and inventory receipts; drug and supply procurement; study billing and invoicing; verifying patient consent; preparing study medications; dispensing inpatient and outpatient prescriptions; preparation and maintenance of drug accountability log sheets; perpetual inventory control; temperature and climate monitoring; development of randomization tables; patient randomization; compliance monitoring; pharmacokinetic calculation and monitoring; patient education; drug study sponsor and regulatory audits and meetings; study closure activities including balancing account records, inventory return to the sponsor and inventory destruction on site, and completion of any other forms or correspondence.

Office: Dr. Meert has a 200 square foot academic office located within CHM. It is equipped with standard office furniture including a desk, conference table, four chairs, credenza and file cabinet; computer; telephone; fax; and hardwired high-speed Internet access. There is also Internet access through the DMC's wireless network. Dr. Meert also has a 220 square foot office for her research assistants located within CHM. The research assistants' office is equipped with standard office furniture, telephones, computers, printers, copying and fax machines, and hard-wired and wireless internet access. The research assistants' office has 3 workstations and additional large file cabinets for storing clinical research files. The research assistants' office is located within the space occupied by the Division of Pediatric Critical Care Medicine. A 250 square foot conference room is also available within the divisional space.

Computer: Dr. Meert has a desktop, laptop and laser jet printer located in her office. The CPCCRN Research Coordinator and other research staff are also equipped with desktop and laptop computers. All critical care attending physicians have computers with Internet access. The PI, research staff and critical care physicians have immediate access to patient data via the DMC-wide Clinical Information System (i.e., electronic medical record). These data are available in the offices of the PI, research staff and physicians, in the PICU, and outside the hospital (e.g., at home) via the Internet. The DMC office of Information Technology provides computer support services to all clinical and academic areas in the DMC including physician and research staff offices.

CMU Clinical Research Institute (CRI) at CHM: The CRI provides research support services to investigators, trainees and research staff through education, research consultation support, data management, statistical analysis, grant administration and regulatory assistance/oversight. For clinical research, the CRI has established a Clinical Research Center (CRC) that has bed space for short-term studies; monitoring equipment and personnel; compliance and regulatory experts; experienced clinical research nursing staff; and managers for contractual and clinical affairs. Additionally, the CRI has wet bench laboratory space for use by researchers. The 6,895 square feet of research lab space within CHM is designed around the concept of an open laboratory to encourage interactions between investigators. The CRI facilities are located within CHM and the DMC University Health Center. The buildings are adjacent to each other and connected by a tunnel. Within CHM, the CRI has approximately 2000 square feet of office space that houses the Grants Management Team and Biostatisticians. The Grants Management Team consists of an Administrative Director, Manager, Sponsored Projects, two Budget Analysts, Grant Pre-Award Administrator and secretarial support. The management team has a

combined 50 years of experience preparing, submitting and managing grants and operational budgets. All administrative and management staff have access to grant management systems which allows them to effectively perform the full range of tasks needed to prepare, submit and manage intramural and extramurally funded grants and budgets. Each staff member has a desktop computer along with a networked printer and scanner. The CRI has two Biostatisticians. Both use fully licensed versions of SPSS and SAS, but have expertise in virtually every statistical and qualitative software package. Each statistician has private office space, desktop computers and access to the networked printer and scanner.

The CRI has an additional 6,000 square feet of research space at DMC University Health Center. This includes 2,000 square feet of administrative office space, 1200 square feet of study participant treatment rooms (6 rooms), 800 square feet for a biospecimen core facility, 700 square feet conference room, and 800 square feet of locked and secure file storage. Additionally, the CRI space at UHC has a private audiovisual conference center. The conference center has ceiling projectors to project videoconference, video, DVD, laboratory, slide, digital X-ray or picture media onto a 110 inch diagonal, tab-tensioned screen and/or a 72 inch diagonal SMART Board interactive whiteboard. The room is wired to hold all needed audiovisual equipment and interactive environment controls.

(4) CHILDREN'S HOSPITAL OF ORANGE COUNTY (CHOC)

Scientific Environment:

THE Saban Research Institute (TSRI) TSRI at CHLA is one of the few freestanding research centers in the U.S. where scientific inquiry is combined with clinical care and is devoted exclusively to children. Our goal is to improve the health and wellness of children through a combination of basic, clinical and translational studies. Research is performed at the lab bench, in the clinic and in the community. TSRI maintains strong scientific and strategic affiliations with the University of Southern California (USC) and, in particular, the Keck School of Medicine of USC. All the Institute's principal investigators (clinical investigators, physician scientists and PhD scientists) are USC faculty, and many have collaborative projects with scientists at the Keck School of Medicine and other departments at USC. The Institute's researchers also are involved in collaborative projects with academic institutions throughout the U.S. and abroad.

TSRI is responsible for providing administrative support for all research activities at CHLA. This facility occupies a total of 198,000 net sq. ft. of research space on the CHLA campus including a 10 story Smith Research Tower, a 5 story Saban Research Building, an 8,000 sq. ft. Clinical Investigation Center, and a 10,000 sq. ft. Community Health, Outcomes and Intervention Research Unit. The Research Institute is home to a centralized Sponsored Projects Office, which is responsible for proposal and award administration as well as financial management. The Institute also supports a series of core facilities fully equipped with state-of-the-art instrumentation to facilitate research at CHLA and USC.

A central initiative of TSRI seeks to understand the childhood and developmental origins of health and disease across the lifespan. The Institute's interdisciplinary research is organized around three synergistic areas of focus that together fully explore the developmental origins of health and disease while addressing the most pressing issues of children's health. These three areas are: The Institute for the Developing Mind; Metabolism, Immunity, Infection and Inflammation; Regenerative Medicine and Cellular Therapies. Research Programs also include 1) Cancer and Blood Diseases, 2) Community, Health Outcomes and Intervention Research, 3) Developmental Biology and Regenerative Medicine, 4) Developmental Neuroscience, 5) Diabetes and Obesity, 6) Human Physiology and Imaging, and 7) Immunology, Infectious Disease and Pathogens. Additionally, TSRI has committed resources to the following strategies in pursuit of our goal of becoming a top 5 nationally ranked stand-alone children's academic health center: 1) recruiting and retaining outstanding junior and senior faculty from all groups; 2) expanding the scientific infrastructure and research facilities to promote synergy and Contact PD/PI: Dean, Jonathan Michael Clinical-Sites--002 (003) Facilities & Other Resources Page 500interaction and to enhance translational research; 3) training and mentoring the next generation of pediatric scientists; and 4) promoting innovative and interactive research.

PICU and Respiratory Research: The Respiratory Research Group at CHLA is an inter-disciplinary collaborative of physicians (critical care, pulmonary, neonatology), nurses, respiratory therapists, biomedical engineers and computer scientists who are committed to conducting respiratory related research projects. Through bi-monthly meetings we discuss and mange a large portfolio of research projects related to respiratory medicine and mechanical ventilation. We have state of the art pulmonary function equipment, some of which we have developed ourselves or in close collaboration with industry, which are used not only for research, but

for advanced clinical monitoring of patients throughout the hospital. We are frequently consulted for our expertise related to respiratory medicine and to assist with comprehensive evaluation of the respiratory system even for patients outside of the intensive care unit. Dr. Newth has been leading respiratory physiology-based studies in our intensive care unit over the last 30 years, with > 50 peer reviewed publications specifically related to lung function testing of patients in our intensive care units. Over the last 10 years, Dr. Khemani has been leading and mentoring trainees on a multitude of studies examining respiratory mechanics and work of breathing from topics related to post extubation upper airway obstruction, non-invasive ventilation, high flow nasal cannula, ventilator weaning, and acute respiratory distress syndrome. CHLA's Division of Pediatric Critical Care has state of the art informatics resources, including real-time data feeds from physiologic patient monitors and ventilators, which are stored on a research server. This enables development of real-time patient applications and requires minimal human data entry.

Clinical Environment

Children's Hospital Orange County (CHOC) Critical Care Research Site: CHOC is a tertiary care Children's Hospital which provides care to more than 185,000 children each year and is home to a wealth of pediatric specialists who have developed pediatric specialty programs and services to meet the needs of our patients. CHOC's pediatric intensive care units provide intensive and acute care to critically ill surgical and medical pediatric patients. The units include an 18-bed PICU on the Nick G. Anas, MD Critical Care Floor located on the 6th floor, including a fully equipped procedure room and a 12-bed PICU on the 2nd floor of the hospital. The Division of Pediatric Critical Care Medicine at Children's Hospital of Orange County routinely cares for children with sepsis and septic shock in our 30-bed pediatric ICU, and 12 bed cardiovascular intensive care unit and we have approximately 2000 admissions to our ICU each year. Our site has years of clinical experience and research infrastructure, and we are confident to be able to identify, enroll and successfully complete evaluations for subjects for the duration of the project. CHOC has a strong track record of participation in multicenter clinical trials in the pediatric intensive care unit and successfully enrolled patients in PALISI Network projects. We have experienced, dedicated research staff available to screen for, recruit and follow research subjects, and we have the capability to manage the clinical specimens required for the study. The clinical research lab is well equipped and set up to facilitate the specimen processing and shipping of biospecimens which will be collected as part of the protocol proposed in this application. The research pharmacy is highly engaged with investigators at CHOC and will be available to process and dispense the study drugs which will be administered as part of this proposal. CHOC Children's and the CHOC Research Institute are committed to providing continued support to the Critical Care Research team by providing the necessary resources including research pharmacy, clinical and research laboratories, nursing staff, respiratory care, administrative support, and translation services to support the activities of CPCCRN.

Children's Hospital Los Angeles (CHLA) is located in the heart of metropolitan Los Angeles, has an established track record of high quality, patient-oriented research and has been the recipient of numerous extramural awards, with a high level of federal funding. CHLA is one of America's premier teaching hospitals through its affiliation since 1932 with the Keck School of Medicine at the University of Southern California (USC) and is among the top 5 in the nation for clinical excellence according to U.S. News & World Report. It has continuously been on the honor roll of top children's hospitals in the country. CHLA is one of the largest children's hospitals in the United States and proudly opened a new state-of-the-art hospital, the Marion and John Anderson Pavilion (see photo) in July 2011, increasing our capacity to 350 beds. CHLA is an active partner in USC's Southern California Clinical and Translational Science Institute (SC CTSI), which is one of the NIH CTSA centers. CHLA is ranked 8th in NIH funding for children's hospitals. CHLA provides care to a large and highly diverse pediatric population, treating more than 104,000 children annually, and admitting more than 13,800 children as inpatients every year, with more than 50% of them under the age of five. Over 16,000 pediatric surgeries are performed annually, including heart and lung transplants, cardiac catheterizations, neurosurgeries and orthopedic procedures. The institution is designated as a Level I Pediatric Trauma Center and provides more pediatric critical care beds than any other hospital in the Western United States. CHLA also hosts one of the largest dedicated transport services in the nation. There is a dedicated helicopter and transports bring patients from all the western states, Hawaii and the Pacific including Japan and Australia. There are over 1800 transports annually staffed by physicians, nurses and respiratory therapists. One of CHLA's overarching aims is to foster innovative research to improve the health and wellness of children through a combination of basic, clinical and translational research studies focused on developing and improving diagnostics and therapeutics and ensuring the delivery of culturally competent care for diverse pediatric populations. This research is conducted under the

auspices of The Saban Research Institute (TSRI), one of the largest and most productive pediatric research facilities in the United States

The Clinical Research Support Office (CRSO) of TSRI, in collaboration with the Southern California Clinical and Translational Science Institute, provides efficient and cost-effective research support to facilitate efficient, high-quality, and safe clinical research and trials throughout CHLA. CRSO staff are experts in implementing, conducting, and monitoring clinical research studies and trials from start-up to close-out, supporting both novice and experienced clinical investigators and study teams. They are available for consultation on CPCCRN trials, although they are not the primary source for staffing.

Research Regulatory Support: While we contain much of the needed regulatory support within the Department of Anesthesiology and Critical Care medicine, TSRI also has Regulatory and IRB Support Specialists to coordinate regulatory affairs for clinical research studies and trials. Support includes: preparation and submission of study protocol to Institutional Review Board (IRB); preparation and filing of Investigational New Drug/Investigational Device Exemption (IND/IDE) initial submissions to the Food and Drug Administration (FDA) as well as yearly reports; and completion of essential study regulatory documents.

Biostatistical Support: Our Biostatisticians support clinical research across CHLA by providing expert consultation services for sample size calculation, analysis of data, and publication development, as well as educating the research community, and collaborating on active research projects.

(5) THE CHILDREN'S HOSPITAL OF PHILADELPHIA (CHOP)

Scientific Environment:

The CHOP Research Institute (CRI): The CRI ranks amongst the top 3 in the nation for NIH research funding support for children and provides robust infrastructure and supervision for clinical research. CRI is one of the largest government- and foundation-supported pediatric research programs in the United States, with more than \$175 million in total federal awards and an annual budget of more than \$600 million (FY21). This continuous support has allowed CHOP to investigate a myriad of pediatric diseases and disorders and emerge as a pioneer in major areas of biomedical and behavioral pediatric research. The Abramson Research Center (ARC) is a 13-story structure housing individual lab spaces and space for core facilities, including gene sequencing, proteomics, microscopy, and nuclear magnetic resonance imaging. In 2010, the 12-story Colket Translational Pediatric Research Building nearly doubled the space available for its more than 500 investigators. Both ARC and Colket contain offices, laboratory space, and resources needed for biostatistical analyses, epidemiological research, and computer-based studies. These committed investigators, institutions, and resources represent leading-edge educators and innovators, who are dedicated to promoting and sustaining safety through knowledge discovery, processing, transfer, and implementation. Clinical research represents the fastest growing research area at CHOP, representing approximately 40% of CHOP's externally funded research.

CHOP Research Institute services include:

The Office of Research Regulatory Affairs is responsible for creating and maintaining procedures to ensure the Protection of Human Subjects. Three Institutional Review Boards (IRBs) conduct initial and continuing review, as well as informing investigators of their obligations and of the procedures by which they submit studies to the IRB for review.

The Research Administration Office is responsible for the final review of all grant applications, ensuring adequate facilities are available to support the application, applicable certifications are provided, and that all applications are signed by an approved institutional representative. This office is also responsible for negotiating on behalf of the institution with all external sponsors, consultants, and subcontractors.

The Research Business Office provides post-award management of grants to investigators. The office consists of an experienced manager who is responsible for the supervision of four senior business managers, seven business managers, three assistant business managers, and three administrative assistants. Services provided include the official authorization of all expenditures, monitoring of all expenses, and provision of internal expenditure reports to investigators of specified grants from the hospital's general accounting-ledger system. The staff is also responsible for working with Research Accounting to ensure that all grants are accurately closed and financial reports are submitted to sponsors in a timely manner.

The Research Accounting Office is responsible for fiscal management of all sponsored projects funds. It maintains a staff of qualified accountants and assistants in performing all accounts receivable and payable functions within the institute. The office generates invoices to external sponsors based on actual expenditures documented in the accounting system operated by the hospital. The staff is also responsible for working with the assigned research business manager to ensure that all grants are accurately closed and financial reports are submitted to sponsors in a timely manner.

Clinical Environment:

The Children's Hospital of Philadelphia (CHOP) has extensive resources to support this proposal. CHOP has more than 28,000 inpatient admissions, approximately 4,000 pediatric intensive care unit (PICU) admissions in the 74-bed PICU, and 100,000 emergency department (ED) visits annually. U.S. News and World Report has consistently rated CHOP in the top 3 in the nation for Pediatrics, with availability of all pediatric subspecialists. As an institution, CHOP is an essential and integral partner of the University of Pennsylvania (Penn) medical system and is adjacent to the Penn Perelman School of Medicine, School of Nursing, School of Engineering, School of Veterinary Science, Wharton School of Business, Annenberg School of Education, and the Hospital of the University of Pennsylvania. There are over 400 faculty and most hold academic appointments at Penn Perelman School of Medicine and participate in the training of medical students, residents, and fellows. CHOP is the community hospital and primary care center for children of Philadelphia and is a major tertiary referral center for the greater Delaware Valley. CHOP has a 560-bed main hospital devoted to inpatient care, the CHOP Research Institute (CRI), the Pediatric Ambulatory Care Center, a medical care and rehabilitation facility for children with chronic illnesses and severe disabilities, and the General Pediatric Faculty Practice which provides primary care. CHOP's Delaware Valley Network includes 26 Pediatric and Adolescent Care Centers, eight Specialty Care Centers, four Primary Care Centers, and four pediatric inpatient units at affiliated community hospitals.

The Department of Anesthesiology and Critical Care Medicine at CHOP consists of more than 120 full-time faculty. The CHOP ICUs alone are staffed by 39 pediatric critical care medicine faculty, 20 pediatric critical care medicine fellows, 100 pediatric residents, and more than 250 pediatric critical care nurses. A dedicated multidisciplinary clinical research team with five full-time research coordinators and several research assistants support more than 20 simultaneous active clinical protocols. With >4,000 PICU admissions/year, the patient care volume at CHOP is supportive of extensive clinical research. This staff is experienced in all types of clinical trials, and provide assistance with protocol development, budget preparation, IRB submissions and regulatory compliance, database development and data collection, and study procedures.

Office: Dr. Fitzgerald has administrative assistance, divisional grants administrative support, and dedicated office space through the Department of Anesthesiology and Critical Care Medicine at CHOP.

Computer: There are substantial computing resources available to the study team. At CHOP, all investigators have a dedicated computer for use with 24/7 information technology (IT) support through the Department of Anesthesiology and Critical Care Medicine. Resources for high level statistical support are within walking distance of the CHOP investigators' primary office spaces either at the Healthcare Analytics Unit or the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics. In addition, computing support is also available through the CHOP Research Institute

(6) CHRISTUS CHILDREN'S HOSPITAL

Scientific Environment:

CHRISTUS Children's is a free-standing children's hospital in the center of downtown San Antonio that provides crucial medical services to more than 150,000 children across Central and South Texas each year. There is a total of 209 beds, including a 60-bed neonatal intensive care unit, a 24-bed pediatric intensive care unit, a 16-bed intermediate care unit and 25 women's services beds.

The Physician Faculty of the CHoSA is provided by Baylor College of Medicine (85%), Pediatrix (10%) and Private Practice Physicians (5%).

The Center for Children and Families at CHoSA houses more than 50 outpatient clinics which serve more than 90,000 children annually. Clinics provide pediatric subspecialty care for children with a wide variety of special medical conditions. Staff includes highly skilled registered nurses, licensed social workers, registered medical assistants, registered dieticians, certified respiratory therapists, Child Life specialists, and licensed physical,

occupational, and speech therapists. Registrars and schedulers are trained to assist patients and families with any questions.

Research Facilities: The Voelcker CRC occupies 11,200 square feet in a stand-alone one-story building located at 414 N. San Saba St., San Antonio, TX 78207. The building is located on the CH of SA campus, approximately 300 yards from the main hospital building. The CRC includes a patient waiting area, an administration office, a dedicated consenting office, four patient exam/treatment rooms, a multi-purpose patient triage room, two patient consultation rooms, a nurses' station, three laboratories, an equipment room, a large file storage room, nine offices, a patient food preparation area, and a staff break room. The space also contains restrooms and hallways, and there is adequate potential for growth.

Clinical Environment:

The exceptionally **large patient rooms** (~250 sq. ft. each) provide ample space to create multifunctional treatment areas, so that each room accommodates a variety of potential research uses. Each patient exam room contains an examination table, an infusion chair, physician table and rolling stool, two chairs for accompanying family members, and a set of table and chairs for children. Three **laboratory spaces** (~300 sq. ft. each) offer apparatus suitable for sample and tissue processing and analysis. Equipment includes bench-top centrifuges, microcentrifuges, tissue culture equipment, molecular biology equipment, microbiology equipment and basic lab ware. The **processing room/nurses work area** (~190 sq. ft.) has a key-pad entry system to maintain security, a refrigerator, and lockable cabinetry suitable for short-term storage of medication. The **equipment room** (~170 sq. ft.) houses two -80°C freezers and two -20°C freezers, with additional space available for liquid nitrogen storage and other equipment. The **patient food preparation area** contains a food refrigerator, a microwave, and other small appliances needed for preparation of dietary items for patients. A **patient seating area** (~325 sq. ft.) provides seating for 25 people. The **patient triage room** contains scales for infants and children, and a phlebotomy chair.

Administrative Support: A large secure **file storage room** (~500 sq. ft.) provides shelving and lockable filing cabinets for storage of protected health information (PHI) and other sensitive materials, tables for sorting paperwork, and adequate space for other materials, supplies and equipment. The **consenting office** (~130 sq. ft.) is furnished with a large desk and consultation space for families to be fully informed and consented to participate in a clinical trial. A large **meeting room** is outfitted with a conference table, seating for twelve, and appropriate AV equipment. A **reception/administration office** (~150 sq. ft.) can accommodate up to 4 administrators. Two **consultation rooms** (~200 sq. ft.) are outfitted with round tables and chairs. Seven **other offices**, ranging in size from ~100 to 200 sq. ft., provide adequate space for the Director, Medical Director and other Associates, and allow space for growth.

(7) MEDICAL UNIVERSITY OF SOUTH CAROLINA (MUSC)

Scientific Environment:

The Medical University of South Carolina (MUSC) is the center of the state's largest medical complex located near the Ashley River on the western border of Charleston, SC. A free-standing academic health center, MUSC is the only tertiary/quaternary care referral center for the entire state. Within a four-block radius of MUSC are the Ralph H. Johnson VA Medical Center, Charleston County Health Department, Charleston Center community addiction treatment program, Roper/St. Francis Healthcare (the area's largest community hospital), and numerous health professional offices and services.

MUSC is the center of the state's largest medical complex, located on the west side of Charleston, SC. A free-standing academic health center, MUSC is the only tertiary/quaternary care referral center for the entire state. Within a four-block radius of MUSC are the Ralph H. Johnson VA Medical Center, Charleston County Health Department, Roper/St. Francis Healthcare (the area's largest community hospital), and numerous health professional offices and services.

MUSC has been at its present site on the Charleston peninsula since 1913, and currently occupies more than 80 acres and 89 buildings. Research buildings at MUSC include: the Basic Sciences Building, a 7-story, 332,000 sq ft laboratory complex that houses MUSC's basic science departments; Darby Children's Research Institute, a 7-story, 122,000 sq ft building housing 14 multidisciplinary lab-based research programs, adjoining the Basic Science Building; the Thurmond Biomedical Research Building, a 7-story, 180,000 sq ft building that contains the Gaze Cardiac Research Institute as well as MUSC and VA research labs and shared facilities; and Walton Research Building, an 8-story, 56,600 sq ft building housing research laboratories for Pathology, Otolaryngology-Head & Neck Surgery, and Pharmaceutical Sciences. Two new research buildings opened in Fall 2011.

Connected to the Basic Science Building via a pedestrian sky-bridge, the Drug Discovery and Bioengineering Buildings add 220,000 sq ft for translational research, research training, and in vivo experimentation. Buildings that include significant research laboratory space, as well as clinical facilities, include the Institute of Psychiatry with nine basic science laboratories for alcohol and substance abuse research and a behavioral animal model facility; the Storm Eye Institute with a 40,000 sq ft Vision Research Center; and the Hollings Cancer Center with more than 200,000 sq ft including 98,000 sq ft dedicated to laboratory-based research.

All laboratory investigators have well-equipped modern laboratories with suitable space for students. Appropriate glassware and sterilization facilities are provided. All researchers at MUSC have access to shared equipment and standard resources such as ultra-low freezers, centrifuges, scintillation counters, and cold, warm, light-controlled, and tissue culture rooms.

Research Cores & Facilities: MUSC has more than 35 state-of-the-art shared research cores & facilities physically housed in and administered by its departments, centers, and institutes. Clinical research faculty, basic scientists, and students all benefit from the shared access to and cost of these research laboratories. Through these diverse resources, MUSC provides access to equipment and instrumentation, technical expertise and training, and education all designed to support innovative, cutting-edge research.

Education: MUSC was founded in 1824 and is the oldest medical school in the southern United States. It has six colleges: Dental Medicine, Graduate Studies, Health Professions, Medicine, Nursing and Pharmacy. MUSC is fully accredited by the Southern Association of Colleges and Schools (SACS) to award bachelor, master, doctoral and professional degrees. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and numerous national, professional, and specialized accrediting bodies provide additional accreditations. Approximately 1,500 faculty members engage in educating more than 3,000 students annually. MUSC awards ~1000 degrees annually with enrollment of >2,500 degree-seeking students. In addition, the university coordinates the training of approximately 80 interns, ~700 residents in six colleges: Dental Medicine, Graduate Studies, Health Professions, Medicine, Nursing, and Pharmacy. For more information on academic programs or clinical services, visit the Medical University of South Carolina. For more information on hospital patient services, visit MUSC Health.

Community: MUSC is the third largest agency in the state and the largest employer in the Charleston area with ~17,000 employees in the University and Medical Center. MUSC leads the South Carolina Area Health Education Consortium (AHEC), linking the academic health sciences center in Charleston to community-based health care centers statewide with an emphasis on health disparities, rural health issues, and access to health care. South Carolina was among the first 11 states to receive federal funding to establish a model statewide AHEC program in 1972. South Carolina AHEC received the prestigious Eugene S. Mayer Award in 2006, presented every two years to the best model statewide AHEC system in the nation. MUSC has received national recognition from the Association of American Medical Colleges and other professional associations for outstanding community service and leadership in innovative health services delivery, outreach, and emergency preparedness.

Siemens Healthineers Partnership: In August 2018, MUSC and Siemens Healthineers announced a first-of-its-kind strategic partnership that will create a blueprint for the rest of the world for a transformed health care system that provides safe, equitable, timely, effective, efficient, and patient-centered care. This partnership will act as an incubator, exposing learners to cutting-edge technology, fostering research inquiry to show whether the clinical changes that MUSC makes influence patient outcomes and stimulating new transformational ideas to change health.

Medtronic and MUSC have partnered to develop value-based health care solutions designed to improve the health outcomes, care experience and cost of health care for patients with chronic diseases and conditions in South Carolina and beyond. The partnership combines Medtronic therapy and technology experience with MUSC's clinical and academic expertise to create a more connected and coordinated care model with shared accountability – focusing on quality of care and putting patients first.

MUSC Innovation Center. A partnership between MUSC, South Carolina Research Authority (SCRA) and the City of Charleston, the Innovation Center supports the sophisticated requirements of Charleston's growing biotechnology cluster organizations whether early-stage or mature. The 28,000 sq. ft. facility, less than a mile from the center of campus, provides research incubator and laboratory space to advance the commercialization of knowledge based on research discoveries and advances in health care.

Innovation: The MUSC Foundation for Research Development (FRD) is an affiliated, not-for-profit, 501(c)(3) corporation, established to manage technology transfer and private sector research relationships for MUSC. FRD is responsible for evaluating all intellectual assets MUSC owns and generates, extracting value, and forging industry and other relationships resulting in products and services that provide real-life solutions to the world's medical needs. MUSC investigators currently submit approximately over 150 new invention disclosures per year, for a total of over 1,900 disclosures since the FRD's inception. On behalf of MUSC and its investigators, FRD has filed more than 500 US patent applications on new technologies. Those applications resulted in over 300 domestic and international patents. In addition, FRD has entered into more than 160 license agreements for MUSC innovations with over 70 products on the market. Over 50 start-up companies have been founded to commercialize MUSC intellectual property. These accomplishments illustrate the quality and practical relevance of MUSC expertise and research findings, setting the pace for future progress. MUSC is also the lead biomedical research institution in Health Sciences South Carolina, a statewide consortium to streamline developing, testing, and bringing health interventions and therapies to widespread use. Through HSSC, the state's three research universities and four largest healthcare systems are integrating research resources, clinical expertise and health and scientific data systems. HSSC has active working groups on science, clinical care, information technology and data interoperability, a statewide IRB, and an integrated Center for Clinical Safety and Effectiveness that develops and coordinates state-of-the-art patient simulation technologies in multiple sites statewide. As the leading research institution in this innovative collaboration, MUSC is ideally situated to develop additional statewide research networks to conduct translational studies and disseminate findings. Statewide collaborations and the relatively small size of the state enable MUSC investigators to rapidly accrue patients in therapeutic, effectiveness and outcomes trials.

Research Training: MUSC offers an outstanding environment for training and career development. The university ranks in the top quartile of domestic educational institutions in the number of NIH grants for research training and education. NIH FY2021 award data include 22 NIH institutional training or research education grants (T32, T35, TL1 and R25 types), 31 NRSA individual fellowships (F-types), 44 individual and 4 institutional career development awards (K12 & KL2 awards), and 12 center grants (P awards) with many including training and career development components for postdoctoral and/or junior faculty. MUSC has three dual degree programs: the NIGMS-funded Medical Scientist Training Program (MD/Ph.D.), the NIDCR-funded Dental Scientist Training Program (DMD/Ph.D.), and PharmD/Ph.D., plus a well-subscribed Master of Science in Clinical Research (MSCR) program that was initiated with K30 support. Four MUSC training programs focus specifically on diversity in the biomedical sciences: the NIGMS-funded Initiative for Maximizing Student Development (IMSD) that supports doctoral training for minorities, two NHLBI R25 grants for short-term research training for minority students, and a Post-Baccalaureate Research Education Program (PREP) that supports minorities in preparation for biomedical research careers.

SmartState® Program: The Smart State Program created by the South Carolina legislature and is funded through South Carolina Education Lottery proceeds. The legislation authorizes the state's three public research institutions, MUSC, Clemson University, and the University of South Carolina, to use state funds to create Centers of Economic Excellence in research areas that will advance South Carolina's economy. The SmartState® Program has resulted in more than \$400 million dollars in non-state investment into the South Carolina economy and is responsible for the creation of 5,000 jobs. To date, MUSC has initiated 20 SmartState® Centers, bringing the total of MUSC endowed chairs and named professorships to 47 (33 appointed as of 2021). In addition to the obvious benefit of providing substantial resources to recruit senior research leadership and entrepreneurship, the program has dramatically raised the profile of university-based research in South Carolina – especially biomedical and clinical/translational research – and stimulated significant philanthropy to meet match requirements.

MUSC Research Growth: MUSC has a substantial research enterprise. In FY2022, MUSC faculty received 1,237 extramural awards totaling over \$297 million. Federal funding (including federal flow-through) constitutes about 66.6 percent of extramural support, with the National Institutes of Health (NIH) as the primary funding agency. With more than \$133 million from the NIH, MUSC's extramural research encompasses: basic research, clinical research, training, and clinical trials. MUSC continues to rank in the top 100 in R&D expenditures at higher education institutions [NSF 2021]. Under the leadership of Dr. Atz as Chair, the Department of Pediatrics has reached the top 40 in NIH funding among Departments of Pediatrics according to the most recent Blueridge rankings.

Clinical Trials Experience: The Divisions of Pediatric Critical Care Medicine and Cardiology at MUSC had a long history of participation in clinical research. MUSC is currently an ancillary site in the NICHD-funded Collaborative Pediatric Critical Care Research Network (1PL1HD105462-01) and one of 9 national centers in the NIH-NHLBI sponsored Pediatric Heart Disease Network (UG1 HL135689). To support clinical research activities, a Pediatric Research Group exists in the Department of Pediatrics which is supervised by a director and two managers and includes 17 full time research coordinators and 4 grant administrators. Our coordinators are very experienced, having managed a wide variety of institutional and industry sponsored multicenter trials.

Protection of Human Subjects: Participation of human subjects in research is under the jurisdiction of federal regulations (45 CFR 46 and 21 CFR 50 and 56). MUSC investigators are granted the privilege of working with human subjects under normal assurance to the government that such research complies with regulations protecting human subjects. The university has a federal-wide assurance for research with human subjects (FWA 00001888, expires 09/07/2021), and is in compliance with federal policy governing use of human subjects. Individuals involved in human subjects research at MUSC are required to complete the Collaborative IRB Training Initiative (CITI) offered online by the University of Miami. All human subject protocols are reviewed through an academic Institutional Review Board (IRB) process that has been accredited by the Association for Accreditation of Human Research Protection Programs (AAHRPP). The MUSC Office of Research Integrity (ORI) coordinates the activities of three IRB committees, involving faculty members as well as representatives of the business, legal, ethical, religious, and civic communities. The MUSC IRB serves as the university affiliate for the Ralph H. Johnson VA Medical Center, which is accredited by the National Committee for Quality Assurance.

Compliance: The MUSC University Compliance Program is a proactive program designed to promote full compliance with all applicable policies, procedures, laws, and regulations. This involves a confidential Compliance Helpline to encourage all members of the MUSC community to ask questions or voice concerns about laws and regulations on such topics as coding and billing, research integrity, professional ethics, human subject/animal research, biological safety, conflict of interests and patient/subject confidentiality. The Compliance Office proactively trains employees, monitors high-risk activities and facilitates discovery of concerns, followed by appropriate investigation and corrective action where appropriate. This program directly assists MUSC's management at all levels in maintaining and enhancing an environment where ethics are paramount considerations in strategic and operational decisions throughout the organization. Institutional research compliances include a training and certification process for all key personnel engaged in research involving human subjects, vertebrate animals or biohazardous substances, as well as integration into curricula of appropriate instruction in the Responsible Conduct of Research (RCR).

South Carolina Clinical & Translational Research Institute: MUSC established the South Carolina Clinical & Translational Research Institute (SCTR) in 2006 in response to the NIH Clinical and Translational Science Award (CTSA) Program, aimed at transforming approaches to research and discovery implementation. The main thrust of the CTSA Program is to catalyze the development of interdisciplinary research initiatives to accelerate the translation of discoveries into improved therapies and clinical practice while breaking down programmatic boundaries.

The SUCCESS Center (Support Center for Clinical & Translational Science) is the “Front Door” of the SCTR Institute, providing comprehensive navigation to all SCTR research support resources, those of the institution and the CTSA National Network. Support spans the entire research spectrum, from inception of ideas through technology transfer and dissemination of best practice models.

The Research Nexus, a key element of SCTR, is a specialized, JCAHO-accredited clinical unit that facilitates patient-oriented research for the NIH and provides medical scientists and trainees with critical resources to advance the understanding of human diseases and enhance therapeutic interventions. The Research Nexus – a 9,200 sqft facility on the 2nd floor of MUSC's Clinical Sciences Building – houses 8 examination rooms, 2 procedure rooms, and a pulmonary function testing suite. A specialized Molecular Core Lab provides services and expertise for studies requiring basic molecular biology (e.g., DNA sequencing) as well as population-based studies (e.g., DHPLC screening). The Research Nexus houses a state-of-the-art facility for cell isolation and processing for local derivation of cells approved for use in human cellular transplantation. For inpatient studies, the Research Nexus uses “scatter-beds” in areas best suited to the needs of the study. SCTR has robust statewide collaborations with affiliate members including the University of South Carolina, Health Sciences South Carolina, Clemson University, Greenwood Genetics Center, South Carolina Research Authority, and the Charleston VA Medical Center.

Clinical Environment:

The MUSC Medical Center operates more than 700 licensed beds in four inpatient facilities – Medical University Hospital (MUH), Shawn Jenkins MUSC Children's Hospital (opened in 2020), Institute of Psychiatry (IOP) and Ashley River Tower – that annually serve approximately 36,000 inpatients and 950,000 outpatients, including 75,000 emergency room visits. MUSC Children's Hospital has consistently been recognized as among the best in the nation by U.S. News & World Report in their annual rankings, with four specialty programs ranked among the top 50 in the nation: Cardiology and Heart Surgery (#4), Nephrology (#30), Cancer (#31) and Gastroenterology and GI Surgery (#41). MUSC has the only Level III neonatal intensive care unit in the region and the only Level 1 pediatric trauma center in the state of South Carolina. MUSC is the only medical center in the state that offers transplant programs for heart, pancreas, kidney-pancreas, small bowel and liver (including living donor procedures for liver transplantation).

Shawn Jenkins Children's Hospital and Pearl Tourville Women's Pavilion: In February 2020, MUSC opened the Shawn Jenkins Children's Hospital and Pearl Tourville Women's Pavilion. This state-of-the-art 625,000 sq. ft. hospital cost \$385 million, span 10-stories, and provides a critically important new space for children, women, mothers, and newborn babies. Shawn Jenkins Children's hospital has 250 licensed beds, increasing capacity by nearly 20% from the previous hospital, 80 licensed NICU beds and dedicated single patient family rooms. SJCH includes a Level 1 trauma center and Emergency Department, the state's only pediatric burn center and solid-organ and bone marrow transplant programs, the state's largest Level 4 neonatal intensive care unit, an advanced maternal-fetal medicine center, and a top-10 ranked U.S. News & World Report children's heart program, which functions through a nationally unique statewide collaboration of pediatric heart surgeons and cardiologists. Atop the building is a helicopter rooftop helio-pad to simultaneously accommodate two Coast Guard helicopters for emergency and disaster situations.

The Pearl Tourville Women's Pavilion has the capacity to manage a full range of obstetrical complexities, include high risk births with access to 36 ante-partum and post-partum mother/baby rooms, 7 couplet care rooms, 2 obstetrical surgical suites, and a dedicated "stork" elevator that takes expectant mothers directly to the maternity pavilion. The integration obstetrical and infant care enhances safety and improves outcomes for high-risk pregnancies.

Built into the hospital are cutting edge technological advancements that enhance provider care and empower the patient experience. Integrated technology includes expanded wireless capability to ensure patients and their families are connected to their friends, family, and community. The hospital has unique telehealth capabilities built into every inpatient room of the facility, except for the neonatal intensive care unit, which employs a cart-based telehealth system.

Access to Patients: The MUSC Medical Center has managed care contracts with all major commercial payers in its area. The tri-county Charleston area is the state's fastest growing region with a population of 665,000 in the primary area and another 500,000 in neighboring areas. As South Carolina's premier health care center, MUSC receives statewide and regional referrals through consortium hospitals, satellite clinics, and an extensive network of referring physicians. In late 2018, MUSC Health announced the purchase of community hospitals located in four rural South Carolina counties. The addition of these hospitals will further extend MUSC's reach into rural and underserved areas where health care access has been significantly limited.

The South Carolina Telehealth Alliance (SCTA): The South Carolina Telehealth Alliance (SCTA) is a statewide collaboration of many organizations joining forces to expand telehealth services across the state. The SCTA provides guidance, assists with strategic development, and advises on technology and standards to develop an open-access network. This open-access network gives all South Carolina residents access to quality health care, while effectively managing the cost of providing care. Extending the vision of telehealth technology to research for areas of high-priority health conditions in SC through an innovative research projects has been highly synergistic with the SCTA strategic plan.

The MUSC Center for Telehealth is one of two federally recognized National Telehealth Centers of Excellence (COE) as awarded by the Health Resources & Services Administration (HRSA), an agency of the U.S. Department of Health and Human Services. MUSC was awarded this national designation because of the Center for Telehealth's successful telehealth programs with a high annual volume of telehealth visits, substantial service to rural and medically underserved populations through telehealth, and its financially sustainable telehealth models. The role of the Center of Excellence is to fill important gaps in the national telehealth landscape through a combination of ongoing regional and national collaborations, as well as proactive dissemination of telehealth resources. The main areas of research focus during the project period include:

- The impact of telehealth on federal and local healthcare spending
- Provider and patient engagement in telehealth
- Development of open access telehealth networks
- Telehealth as a model for implementation of best clinical practices
- Behavioral health-focused telehealth programs
- Telehealth modalities for primary care (i.e. developing a “Primary Care Telehealth Menu”)

Research Administration: The MUSC research infrastructure includes pre-and post-award functions reporting to the Vice President of Research. The Office of Research Development (ORD) focuses on program and proposal development, identifies funding opportunities, develops proposal concepts, networks faculty members with complimentary interests, provides grant-writing consultation and workshops, offers pre-submission critiques, compiles institutional data, and prepares competitive proposals for research infrastructure, and research training. The Office of Research and Sponsored Programs (ORSP) handles certifications and assurances, ensures that policies and procedures are followed, helps prepare budgets, negotiates terms and conditions, maintains proposal and awards data, and oversees re-budgeting and close-out activities. ORSP is the institutional interface with Grants.gov and coordinates all aspects of electronic research administration. The Office of Research Integrity (ORI) provides oversight and staffing for activities focused on compliance with regulations for research involving humans, vertebrate animals, and biohazardous agents. It also coordinates the management of conflicts of interest, financial disclosure, and scientific integrity issues. The Office of Clinical Research (OCR) supports physician-scientists by developing strategic partnerships with industry sponsors, supporting feasibility and site selection processes, and employing metric tracking and reporting to ensure efficient study activation timelines, improved participant accrual, and optimal financial performance.

Electronic Institutional Review Board (eIRB): The Electronic Institutional Review Board (eIRB) system is a statewide platform that simplifies the permission and review process for biomedical research projects. HSSC developed and hosts for its members an eIRB platform to enable coordinated review of research projects, assuring compliance with state and federal laws. Seven of the 8 IRBs across HSSC member organizations use the eIRB platform for the conduct of their individual IRBs. In establishing this system, leaders from the IRBs across the state have agreed upon workflow and forms for more than 80% of all IRB submissions. In continuous improvement and learning, the groups convene regularly to harmonize activities, in order to facilitate research. Investigators may seek permission to conduct a research at each individual HSSC supported organization, and enable that same documentation and protocol to be used and viewed by IRBs at other organizations. This greatly decreases the work of collaborating researchers. Additionally, IRBs may elect to allow another IRB to serve as the IRB of record, in a true cooperative review, and further enhance the ability for increased statewide research collaboration projects. In the most recent year, there were more than 6,650 active studies within the eIRB system, with more than 4,500 unique users.

Computer: Participating faculty and students have desktop computers with network access to computerized clinical data management systems, outpatient electronic medical records, Lanvision, Access Anywhere, IDX registration system, and the integrated laboratory system. Statistical software includes Epistat, SAS, SPSS, S-Plus, and M-Plus. DXCG and ACG software are available for patient case mix analysis. MUSC Information Solutions provides information technology, informatics, and analytics services for the academic health center. It manages the campus-wide data and voice communication network as well as other core infrastructure systems and applications, with high-speed ethernet network and internet support with wireless access throughout the campus. Main infrastructure systems include Microsoft Exchange email, file storage, web servers, calendars, network identification and account maintenance, network time protocol, domain name system, and directory services. Core academic applications include the MUSC Library System, OVID, WebCT, SYBYL (molecular modeling), and GCG (gene sequence research). Core financial and administrative applications include GL, AP, financial reporting, purchasing, payroll, and human resources. The Division of Pediatric Cardiology employs two fulltime information technology professionals (a network manager and a computer programmer / database specialist).

MUSC Data Network and Security: Access outside the MUSC firewall requires a VPN with two-factor verification. Free encryption service is provided for all laptops. Other data security elements include enterprise Public Key Infrastructure (PKI) service, advanced intrusion detection systems (IDS), Security Information and Event Management system (SIEM), and virtual machines (VMs) for research data management and analysis. Enterprise-wide process improvements include network access control, technical vulnerability management program and Data Center physical security. The MUSC Data Center is manned 24x7 by operations staff who monitor all servers, environmental conditions, and notify appropriate personnel as needed. The entire Data

Center is protected by a card access system and 24-hr security cameras at each door entering and within the center. Weekly full-verified backup, daily differential verified backup, and every-6-hr transaction log backup are captured by IBM® TSM system, Microsoft® Volume Shadow Copy service, and Microsoft® SQL server, so that a new system can be restored using the backup tapes/files with minimal data loss in case of a catastrophic failure to a web or database server. The university system is backed up on a nightly basis, data files are written initially to disk and staged to tape. Copies of the tapes are rotated offsite to vital records (3 months of taped backups are available at any given time). In the event of hurricanes or other natural disasters, two forms of backups will be performed to ensure that data are not lost: 1) the information system will keep timely backups available at the remote site, and 2) project personnel will be instructed to bring updated copies of their data on external hard-drives if evacuated.

Diversity, Equity, and Inclusion: MUSC is committed to providing culturally competent care and ensuring that organizational priorities and goals pertaining to equity, inclusion, and excellence are institutionalized, sustained, and measured to “create an inclusive experience for the lives we touch.” The Interim Chief Equity Officer for MUSC is Willette Burnham-Williams, PhD. Every college has a designated faculty liaison for diversity, and all leaders are required to complete diversity education and training to combat unconscious bias on an annual basis. All new employee orientations include an introduction to MUSC’s diversity goals and values.

For two consecutive years (2018 & 2019), Forbes has listed MUSC as one of America’s Best Employers for Diversity. MUSC ranked 13 out of 500 organizations. Moreover, MUSC ranked number 3 out of 30 institutions listed in the education category. Additionally, for four years in a row (2017 – 2020) MUSC has received the Health Professions Higher Education Excellence in Diversity (HEED) Award from INSIGHT in Diversity, the oldest and largest diversity- focused publication in higher education. The organization has also designated MUSC a Diversity Champion for three consecutive years (2018 – 2020). MUSC was among 46 recipients selected in 2020 for this honor, which is the only national diversity award in higher education. In December 2017, the South Carolina Chamber of Commerce named MUSC the recipient of the 2017 Excellence in Workplace Diversity in the category for medium and large business. In 2016, MUSC Health was named a leader in LGBTQ Healthcare Equity by the Human Rights Campaign Foundation, the educational arm of the nation’s largest lesbian, gay, bisexual, and transgender civil rights organization. In 2015, MUSC received the national Leadership Award of the Group on Women in Medicine and Science (GWIMS) of the American Association of Medical Colleges (AAMC). In addition, MUSC’s College of Medicine received an ADVANCE grant from the National Science Foundation for the Advancement, Recruitment and Retention of Women in Science (ARROWS), the only such NSF grant awarded to an academic medical center. Furthermore, the AAMC ranks MUSC in the 97th percentile among medical schools preparing physicians to care for patients of different backgrounds.

(8) NATIONWIDE CHILDREN'S HOSPITAL

Scientific Environment:

Nationwide Children's Hospital is the second largest children's hospital in the United States, with > 500 inpatient beds and >1.6 million patient visits annually. It is the sole quaternary care provider to the largest catchment area in Ohio, though children came from all over the world to receive care. We were once again listed on the U.S. News & World Report's Best Children's Hospital Honor Roll for 2022-2023, a distinction awarded to only a select few children's centers in the U.S. We offer the full array of medical and surgical subspecialty services including bone marrow and solid organ transplantation. The Division of Critical Care Medicine at Nationwide Children's Hospital includes 30 faculty members and a total of 12 fellows (4 per year) dedicated to the advancing the care of critically ill children.

Clinical Environment:

The Pediatric Intensive Care Unit (PICU) at Nationwide Children's Hospital: at NCH is a 54-bed multi-disciplinary medical/surgical (non-cardiac) ICU that sees > 3,000 admissions per year, making it one of the largest PICUs in the country. Nationwide Children's Hospital serves the largest pediatric Level I trauma catchment area in Ohio and is home to robust, accredited Level I trauma and burn programs. We have the capability to manage the highest levels of complexity and acuity including advanced modes of mechanical ventilation, continuous renal replacement therapies, and extracorporeal membrane oxygenation support. During daylight hours, the PICU is staffed with three teams, each led by a BC/BE attending pediatric intensivist who has successfully completed a three-year PCCM fellowship. In addition to faculty leadership, each team has 1-2 critical care medicine fellows and/or advanced practice nurses (APN), plus residents from our categorical pediatrics, internal medicine-pediatrics, and/or dual (MD/DO) training programs. The ICU teams have dedicated

ICU pharmacists, ICU nutritionists, and an ICU care coordinator. Nighttime coverage in the PICU is provided by 1-2 in-house BC/BE attending pediatric intensivists (different from the daytime on-service attendings) plus 1-2 critical care medicine fellows and 3-4 residents and/or advanced practice nurses. The PICU includes a 120 square foot "in-unit" research laboratory space that contains ample equipment to perform sample processing including centrifugation, pipetting, incubation, cell culture, and refrigerator/freezer storage.

The Cardiothoracic (CT)-ICU at Nationwide Children's Hospital: is a 20-bed unit dedicated to the care of children with medical heart disease and/or surgical cardiothoracic disease (e.g. congenital heart disease, lung transplantation). The CTICU sees >500 admissions per year including >350 post-operative cases requiring cardiopulmonary bypass. All of the advanced therapeutic and supportive modalities that are available in the PICU are available in the CTICU, which is staffed during daylight and nighttime hours with a team led by a pediatric cardiac intensivist. Advanced practice nurses and PCCM and/or cardiology fellows participate on daytime and nighttime teams.

Critical Care Medicine Research Coordinators : The Division of Critical Care Medicine at Nationwide Children's Hospital has five full-time research coordinators, all of whom have backgrounds in pediatric critical care nursing. They are expert in the conduct of clinical and translational research in the pediatric ICU including subject identification and enrollment, sample collection and processing, clinical data collection, and regulatory compliance. Our research coordinator core provides 7-day/week study on-site study coverage and can provide overnight coverage as needed.

Office: Dr. Hall has an office on the Nationwide Children's Hospital campus in the Division of Critical Care Medicine, and in close proximity to the Immune Surveillance Laboratory.

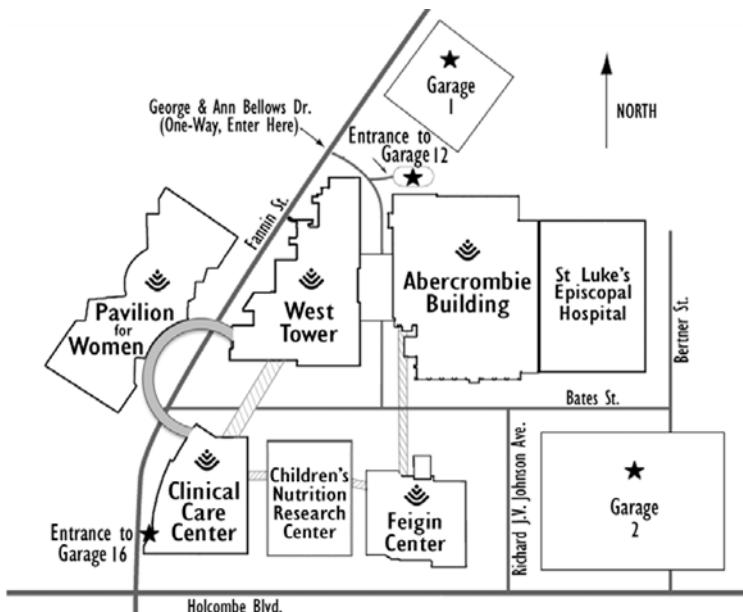
Computer: Dr. Hall has two desktop PCs in the Immune Surveillance Laboratory in addition to a PC in his personal office. He has adequate software and support for word processing, spreadsheeting, advanced statistical analysis, and graphing.

(9) TEXAS CHILDREN'S HOSPITAL

Clinical Environment:

Texas Children's Hospital, located in Houston, Texas, is a not-for-profit organization whose mission is to create a healthier future for children and women throughout our global community by leading in patient care, education, and research.

Main Campus: Texas Children's Hospital (TCH) is one the largest children's hospital in the United States and the primary teaching hospital for Baylor College of Medicine, Houston, TX. This full-care, state-of-the-art facility provides inpatient and outpatient care in more than 40 specialties and subspecialties with more than 800 licensed beds across three campuses, of which a total of 163 are intensive care unit beds with >6000 annual admissions to the intensive care units. The main Texas Children's Hospital main campus consists of a nine-building complex that includes: (a) the Abercrombie Building, devoted to a variety of administrative and patient-oriented uses; (b) the West Tower, where the emergency department, neonatal intensive care unit, operating rooms, inpatient beds, and Clinical Research Center are located; (c) a 16-story Clinical Care Center, that houses all out-patient clinics; (d) the Children's Nutrition Research Center, dedicated to nutrition research in the neonate, infant and child; (e) the recently renovated 20- story Feigin Center, which provides a total of 540,010 sq. ft. of space for state-of-the-art pediatric research initiatives including the Sabin Vaccine Institute and a GMP facility for cell and gene therapies; (f) the Neurological Research Institute, the world's first basic research institute dedicated to childhood neurological diseases, opened in the Spring of 2011 (not shown on map, a 5 minute walk from the Feigin Center); (g) Texas Children's Pavilion for Women (opened in the Spring of 2012 and connected by a two-story walkway to the Clinical Care Center and West tower), where gynecologists, obstetricians and



neonatologists provide women, mothers and babies with a full continuum of high-quality care, and (h) (adjacent to Pavilion for Women) the Legacy Tower, opened May 2018, a 23 story building housing pediatric intensive care units, cardiac intensive care units, heart center, state of the operating rooms, as well as a helipad for transport of critically ill children.

In 2018, we opened the Lester and Sue Smith Legacy Tower at the Texas Medical Center Campus. This state of the art 640,000 sq. ft. tower houses 163 pediatric and pediatric cardiac ICU beds over seven ICU floors, with two dedicated MRI scanners, as well as all of the high-acuity general, transplant, neurosurgical major surgical operating rooms. The entire Heart Center including catheterization laboratory and dedicated cardiac operating rooms is also collocated in this tower. The ICU rooms are large (350-450 sq. ft. of clinical space), with state-of-the-art equipment and additional dedicated family space. All rooms are equipped for dialysis, and were designed to provide sufficient space for infants, children or young adults requiring simultaneously multiple modalities of mechanical and extracorporeal support, as well as urgent imaging.

Texas Children's Hospital provides all pediatric subspecialty services which include critical care medicine, surgical critical care, trauma, neurosurgery, neurology, rehabilitation, pathology, transfusion medicine, thrombosis and hemostasis, pathologic immune activation, radiology, interventional radiology, immunology, pulmonology, cardiology, pharmacology, nutrition, rheumatology, nephrology, gastroenterology, hematology/oncology, genetics, infectious diseases, allergy, dermatology, endocrinology, child development, otolaryngology, pediatric plastic surgery, orthopedics, anesthesiology, cardiothoracic surgery, and solid organ and stem cell / bone marrow transplantation. As a level I trauma center, dedicated space for trauma cases is available in the Emergency Center, our main operating room suite, intensive care and inpatient units.

To coordinate incoming patient flow, experienced pediatric intensivists command a state-of-the-art communications center called **Mission Control** 24/7. These intensivists also act as medical control for the specialized transport team Kangaroo Crew that provides ground and air transport for continental and international transports. Mission Control is a 3,500-square-foot high-tech command center used as unified operations center bringing together critical care admissions, hospital-to-hospital transfers, critical clinical alarm monitoring security, facilities, code response, and room management. Fully opened in 2017 and staffed by critical care physicians, Mission Control has been instrumental in reducing transportation times, improving the patient-acceptance process, optimizing system communications and was recognized by the American Society for Healthcare Engineering (ASHE) receiving ASHE's 2017 Excellence in Health Care Facility Management Award. The visual displays allow monitoring in real-time patient census in all campuses, admissions/discharges, locations of ambulances, status of helipads, weather and road conditions and other critical information to empower the medical control of transport to facilitate optimal disposition and expedite patient flow.

Texas Children's Hospital houses active, innovative and highly regarded extracorporeal therapy programs that provide cardiac, pulmonary, renal and liver support as a bridge to both transplantation and recovery, and is widely recognized as a leader in the field. We are consistently amongst the three most active solid organ transplant programs in North America, performing between 90 and 100 transplants annually in infants, children and young adults, including more than 30 liver transplants and over 20 heart transplants. A significant proportion of our patients have been denied transplant by other prominent centers due to medical complexity or overall risk. We have one of the most active ECMO programs in the nation, typically supporting between 45 and 60 patients from newborns to older children annually, with life-threatening cardiac, pulmonary or cardiopulmonary failure., Awarded Gold Status by the Extracorporeal Life Support Organization (ELSO) Registry in 2019, our ECMO program includes a Critical Care ECMO consult team and a transport service. Our ECMO transport team of intensivists, surgeons, ECMO specialists, and transport personnel provides round- the-clock air and road transport of patients already on ECMO, as well as the option of cannulating unstable patients at the referral center, for transfer to Texas Children's Hospital for ongoing management.

The Texas Children's Heart Center houses the nations most active ventricular assist device (VAD) program, providing bridging support in more than ten patients annually. In addition, our center is considered amongst the most innovative in the nation, and is at the cutting edge of device development and new device introduction. Examples include our role in the PUMPKIN trial (introducing a miniaturized paracorporeal device for infants and small children with end-stage heart failure who are failing conventional management, and our extensive use of the IMPELLA VAD device to provide temporary support for ventricular failure and myocardial decompression in patients with acute or acute-on-chronic heart failure.

The Texas Children's Hospital Renal Dialysis and Apheresis services provide over 6000 treatments annually, to children of varying ages ranging from neonates to young adults. All modalities of acute dialysis are provided within our center under the direction of the Critical Care Nephrology program, an unparalleled unique program in pediatrics. CRRT program has 1200-1500 days annually. In addition, we have developed the nation's first pediatric Liver ICU team and consult service that provides multidisciplinary, multimodality hybrid extracorporeal liver support (ELS) to infants and children with liver failure. Our ELS program that utilizes albumin-augmented dialysis is one of only three active pediatric centers and is the largest and busiest in the nation, adult centers included. Hybrid extracorporeal therapy, where CRRT, TPE, and ELS are combined in patients with acute liver failure and acute or chronic liver failure to provide support through multiple organ failure and bridge to transplantation or recovery is exclusive to our center. Additionally, the Critical Care Nephrology program, under the direction of our PI, operates a multidimensional quality program modeled after active surveillance for patient safety.

The Texas Children's Hospital Investigational Drug Service (IDS) pharmacy supports clinical trials for all pediatric subspecialties. The Pharmacy is experienced in the support of all types of clinical trials, including those involving investigational agents or requiring special preparation, packaging, or labeling for blinded or randomized studies. Two dedicated pharmacists and one pharmacy technician staff the IDS. The Investigational Drug Service occupies space distinct from the central pharmacy, has adequate storage capabilities and dedicated cold storage and freezer space. It has the responsibilities for randomizing patients onto clinical trials, controlling distribution of study agents, and maintaining accountability of study drugs. The Investigational Drug Pharmacist reviews all protocols that include investigational drugs and must sign off on them prior to IRB approval. Similarly Research Pharmacy support at CHoSA includes clinical trial drug regulatory compliance, dispensation of investigational products, randomization and study drug accountability, and integrity of blinding.

Clinical Research Center at Texas Children's Hospital

Investigators have access to the Clinical Research Center (CRC) at Texas Children's Hospital, which hosts a discrete inpatient and outpatient research unit to accommodate investigator needs. The CRC has been in operation for over 48 years and is currently supported through Texas Children's Hospital. The CRC has a 6 bed pediatric inpatient unit, 6 outpatient rooms, 1 room for metabolic studies and a fully operational metabolic kitchen. The CRC is staffed 24 hours per day 5 days per week and on alternating weekends, by specially trained research nurses, dietary staff, and administrative personnel. The CRC offers use of its facilities and resources for clinical studies, which have been approved through the Baylor IRB and the CRC Scientific Advisory Committee. The research team is all CITI-certified and receives research onboarding, which includes Good Clinical Practice, Code of Federal Regulations, BCM research policies, and local CHoSA standard operating procedures. Research protocols undergo an institutional feasibility review process in which protocols are diligently reviewed to ensure adequate resources, both technological and human, will successfully support the project. Bedside nursing, pharmacy and local laboratory research needs are supported by CHoSA associates.

The Voelcker CRC occupies 11,200 square feet in a stand-alone one-story building located at 414 N. San Saba St., San Antonio, TX 78207. The building is located on the CHoSA campus, approximately 300 yards from the main hospital building. The CHoSA CRC includes a patient waiting area, an administration office, a dedicated consenting office, four patient exam/treatment rooms, a multi-purpose patient triage room, two patient consultation rooms, a nurses' station, three laboratories, an equipment room, a large file storage room, nine offices, a patient food preparation area, and a staff break room. The space also contains restrooms and hallways, and there is adequate potential for growth.

The exceptionally **large patient rooms** (~250 sq. ft. each) provide ample space to create multifunctional treatment areas, so that each room accommodates a variety of potential research uses. Each patient exam room contains an examination table, an infusion chair, physician table and rolling stool, two chairs for accompanying family members, and a set of table and chairs for children. Three **laboratory spaces** (~300 sq. ft. each) offer apparatus suitable for sample and tissue processing and analysis. Equipment includes bench-top centrifuges, microcentrifuges, tissue culture equipment, molecular biology equipment, microbiology equipment and basic lab ware. The **patient food preparation area** contains a food refrigerator, a microwave, and other small appliances needed for preparation of dietary items for patients. A **patient seating area** (~325 sq. ft.) provides seating for 25 people. The **patient triage room** contains scales for infants and children, and a phlebotomy chair. A large secure **file storage room** (~500 sq. ft.) provides shelving and lockable filing cabinets for storage of protected health information (PHI) and other sensitive materials, tables for sorting paperwork, and adequate space for other materials, supplies and equipment. The **consenting office** (~130 sq. ft.) is furnished with a large desk and consultation space for families to be fully informed and consented to participate in a clinical trial. A large **meeting**

room is outfitted with a conference table, seating for twelve, and appropriate AV equipment. A **reception/administration office** (~150 sq. ft.) can accommodate up to 4 administrators. Two **consultation rooms** (~200 sq. ft.) are outfitted with round tables and chairs. Seven **other offices**, ranging in size from ~100 to 200 sq. ft., provide adequate space for the Director, Medical Director and other Associates, and allow space for growth.

The current CHoSA research portfolio as of 06/01/2020 includes 136 active research projects of which are 48% interventional, 19% chart review, 10% registry, 8% educational, 5% biology, 5% observational and 5% survey studies. Out of these 136 active research projects, 46% have associated extramural funding.

CHoSA management of grants and subcontracts is handled by both the on-site Director of Clinical Research, and the Office of Sponsored Programs at the CHRISTUS Institute for Innovation and Advanced Clinical Care (CIIACC) located at the CHRISTUS Health corporate offices in Irving, TX.

Investigators also have access to resources from the Office of Research at BCM, including The Office of Research IT (ORIT), which provides a broad range of data systems, resources, and services to support the research and data needs of basic, clinical and translational BCM investigators.

(10) UNIVERSITY HOSPITAL'S RAINBOW BABIES AND CHILDREN'S HOSPITAL (RBC)

Scientific Environment:

RBC is a 224-bed quaternary care pediatric referral center and is the **only free-standing children's hospital in the Cleveland-Elyria Metropolitan Area**, which has a population of 2 million people. RBC **ranks among the nation's top 50 children's hospitals in all specialties per US News and World Report**, including cancer, diabetes and endocrinology, gastroenterology and GI surgery, neonatology, nephrology, orthopedics, pulmonology and urology. RBC is consistently one of the most well-funded Departments of Pediatrics in the country. The **20-bed pediatric intensive care unit (PICU)** at RBC is a multi-disciplinary quaternary care unit that includes both cardiac and non-cardiac patient populations and **sees over 1,600 admissions per year**. A separate 12-bed pediatric cardiac intensive care unit (PCICU) is opening in late Fall, 2023. The PICU at RBC is staffed 24/7 by BC/BE pediatric intensivists along with fellows. There are a total of **17 Pediatric Intensivists** on faculty along with nine PICU Fellows. Most of the Intensivists participate in research, and the PICU research program is co-directed by Drs. Steven Shein and Kenneth Remy. There are currently **several on-going, federally funded, multicenter research projects** in the RBC PICU, including PARADIGM, PRECISE, PICFlu, Overcoming COVID, AMPLE and PICS-p. Day-to-day activities are performed by a **team of research coordinators, research nurses, data managers and a PICU research program manager**. The PICU research program utilizes UH Clinical Research Center resources and resources from CWRU to administer federally funded grants.

Clinical Environment:

RBC is part of University Hospitals (UH), a non-profit entity that was founded in **1866**. There are currently **18** hospitals, including 3 joint ventures. UH offers the **largest** primary care network in the region. There are **50+** health centers, freestanding urgent care and convenient care centers, and surgery centers. There are **6** facilities providing behavioral, elder, home care, rehabilitation and integrative health services. UH is Ohio's largest employer, with over **4,000** volunteers. UH is dedicated to academic research, with more than **2,100+** active clinical studies, including **600+** interventional clinical trials under way. UH is a top choice for industry sponsored research in Northeast Ohio with over **700** active Principal Investigators experienced in a wide range of specialties. With more than \$187 million in funding from the National Institutes of Health and joint UH-CWRU clinical and translational research projects, UH-CWRU forms the largest center for biomedical research in the state of Ohio. UH-CWRU also have the unique capacity to conduct pragmatic clinical trials merging EMR data among the three health systems in Northeast Ohio, effectively creating a closed system to track outcomes.

UH Clinical Research Center (UH CRC): is the central administrative office for all clinical research studies conducted within the system. UH CRC is comprised of eight core offices offering an array of support ranging from research education, IRB administration, study team staffing and specialty equipment through full-spectrum research accounting & finance.

University Hospitals Cleveland Medical Center Institutional Review Board: Federal guidelines require IRB approval prior to the conduct of any Human Subjects Research. The UH IRB administration office facilitates the

review of Human Subjects Research that involves UH patients, data, property, or systems. The IRB administration office will pre-review submissions before forwarding to an IRB Chairperson or Board for review. Each UH department is assigned a specific IRB Specialist to help streamline communication and submission. In general, IRB specialists can provide assistance navigating the electronic submission system, and may offer guidance on modifying a research proposal to comply with federal and local regulations. The IRB Administration Office provides regularly scheduled education sessions, and will provide targeted education sessions upon request. For personalized assistance, the IRB Administration Office offers weekly walk-in hours, and will make appointments upon request.

The IRB Administration Office also offers the services of an IRB Support Specialist. The IRB Support Specialist will meet with you and guide you to appropriate policies, templates, and resources necessary for a complete submission, likely minimizing the number of reviewer stipulations and time to approval. This support is limited to new studies and is reserved primarily for research studies conducted by new UH investigators and UH faculty or UH trainees submitting investigator-initiated drug and device trials. The UH IRB has three committees and holds at least 6 meetings per month in order to facilitate the efficient review of research.

UH Research Finance: The Research Finance Specialist (RFS) core is dedicated to assuring fiscally sound clinical research budgets and Medicare compliant research-related patient care billing. Working in conjunction with the Grants and Contracts core, and in collaboration with the department, the Research Finance Specialist will develop the patient care budget and billing coverage analysis for a clinical study. The Research Finance Specialist will incorporate budget quotes from ancillary service areas and assure that UHLSF research requisitions are set-up prior to first patient enrollment. If a study involves the use of an investigational drug, biologic, or device, the Research Finance Specialist will assure appropriate set-up for billing, and in the case of investigational devices, guide the department in completing the necessary Medicare Administrative Contractor paperwork.

(11) THE UNIVERSITY OF CALIFORNIA, DAVIS HEALTH

Scientific Environment:

The University of California Davis Health is improving lives and transforming health care by providing excellent patient care, conducting groundbreaking research, fostering interprofessional education, and creating dynamic, productive partnerships with the community. As the region's only academic health center, UC Davis Health is a hub of innovation that encompasses the UC Davis Medical Center, the UC Davis School of Medicine, the Betty Irene Moore School of Nursing, and the UC Davis Medical Group. UC Davis Health is located on a 140-acre campus in Sacramento, only minutes from California's capital. Collaborative research is the hallmark of UC Davis. Major areas of research growth include innovative programs that focus on improving individual, family, community, and population health such as the UC Davis Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, which has been named an NIH Intellectual and Developmental Disabilities Research Center, one of only 15 nationally.

Clinical Environment:

UC Davis Children's Hospital has the Central Valley's only Level 1 pediatric trauma center and emergency department, and the 129-bed hospital includes neonatal, 24 bed pediatric, and pediatric cardiac intensive care units. It is also home to the first Level 1 children's surgery center on the West Coast and fourth in the nation, as noted by the American College of Surgeons. In Fall 2018, the new UC Davis Children's Surgery Center opened. This state-of-the-art pediatric facility includes seven larger and more effectively designed operating rooms, a technologically advanced fleet of surgical equipment, and 24 pre- and post-op bays. It offers the broadest range of pediatric specialty care in the region, with faculty physicians certified in more than 37 areas of pediatric medicine.



The UC Davis Center for Health and Technology offers a unique group of services including telemedicine, simulation, education, research, and media production. The Center is housed in a 52,000 square foot building with state-of-the-art facilities to support virtual training in medicine and is one of the University of California's premiere facilities for developing innovations in telemedicine, clinical care, health research, and medical education. The Telehealth Program provides direct clinical care to patients at a distance. Since the inception of the program, real-time consultation services have been offered in more than 40 specialties linked to over 100 clinics and hospitals, the majority of which are located in, or provide services to, rural areas.

The Clinical Telehealth Program at UC Davis Health provides a number of adult and pediatric specialty services throughout the state of California. Connecting rural physicians and their patients to renowned specialists is a hallmark of the UC Davis program. Clinical Telehealth provides rural physicians, who typically do not have specialty training, real-time access to experienced physicians at UC Davis Health. The pediatric telemedicine program encompasses a dedicated, multidisciplinary team of physicians, nurses, researchers, technology experts, and administrators working together to provide high quality care.

Office: The principal investigator and co-investigators involved in this proposal have office space available on UCSF's Mission Bay and Oakland campuses, UCLA and UC Davis. Full office support with dedicated research associates and an academic assistant is also available. Office space includes a combination of private offices, shared offices and, cubicles for post-graduate fellows, graduate students and other administrative and support staff.

Computer: The UCSF Department of Pediatrics has a research computing facility that provides a core infrastructure for networking and systems administration. The staff that are supported by this facility manage Mac laptops for research and investigators running OSX for data storage and generation of reports, and a number of Sun UNIX workstations.

All of the computer workstations and servers have the necessary software tools to perform research data management. As members of the California Quantitative Institute of Biosciences (QBI), we have access to 4000+ nodes of high-performance computing cluster for data processing. Office: The principal investigator and co-investigators involved in this proposal have office space available on UCSF's Mission Bay and Oakland campuses, UCLA and UC Davis. Full office support with dedicated research associates and an academic assistant is also available. Office space includes a combination of private offices, shared offices and cubicles for post graduate fellows, graduate students and other administrative and support staff.

(12) THE UNIVERSITY OF PITTSBURG SCHOOL OF MEDICINE

Scientific Environment:

UPMC is a world-renowned, nonprofit health care provider and insurer committed to delivering exceptional, people-centered care and community services. Headquartered in Pittsburgh and affiliated with the University of Pittsburgh Schools of the Health Sciences, UPMC is shaping the future of health through clinical and technological innovation, research, and education. Dedicated to advancing the well-being of our diverse communities, we provide more than \$1 billion every year in community benefits, more than any other health system in Pennsylvania. Our 95,000 employees — including more than 5,000 physicians — care for patients across 40 hospitals and 800 doctors' offices and outpatient sites in Pennsylvania, New York, and Maryland, as well as overseas. UPMC Insurance Services covers 4.5 million members with a focus on providing the highest-quality care at the most affordable price.

The Pediatric Clinical and Translational Research Center (PCTRC): is a multidisciplinary center that provides physicians the opportunity to investigate childhood diseases in a controlled environment in both an inpatient and outpatient setting.

It is one of only a few centers in the nation that is funded by the National Institutes of Health (NIH) and is devoted to pediatric research. It received this distinction in 2006 when the University of Pittsburgh was selected as part of the group of 12 institutions to form NIH's Clinical and Translational Research Consortium.

The PCTRC's is based on Children's former General Clinical Research Center, or GCRC which was established in 1962, supporting research for 58 years with a staff of physicians, nurses and other health care professionals dedicated to supporting children and families participating in research initiatives.

The PCTRCC has facilities capable of accommodating both inpatient and outpatient settings. It is sponsored by the National Institutes of Health and National Center for Advancing Translational Sciences.

The PCTRCC is located on Floor 3 of the Administrative Office Building at Children's Hospital of Pittsburgh of UPMC, accessible via the pedestrian bridge from Floor 3 of the main hospital building.

Laboratory: The PI ,Joseph Carcillo MD, will have the support of Critical Care Laboratories which is approximately 5000 square feet of newly renovated research space on the 10th floor of Scaife Hall, on the University of Pittsburgh Main Campus. These facilities are capable of supporting the proposed studies in this application. This area will be used to quality control store processed blood samples and for performing enzyme -linked immunosorbent assays (ELISA). This laboratory has run assays for several large multicenter projects and is capable of supporting the proposed laboratory work in this application. These spaces will provide ample bench and desk space, fume hoods, sterile culture hood, and space for all required equipment. The whole blood ex vivo kits (culture media plus a known amount of salmonella endotoxin) will be assembled here for shipment to the participating sites. In this lab, researchers have the ability to process blood samples, perform any required extraction procedures on plasma, perform assays by HPLC, ELISA, LUMINEX®, spectrophotometric, luminometric, and enzyme cycling methodologies.

The PI also has a 100 square feet clinical research laboratory next to the Pediatric Intensive Care Unit at the Children's Hospital of Pittsburgh for blood and culture specimen processing prior to transport to the base laboratory at Scaife Hall.

The computers in the laboratory are networked through the Departmental Information Services Department. Barcode scanners and computers are used throughout the laboratory area for sample tracking and inventory. A custom tracking system has been built by the CRISMA Data Management Team to track specimens during all procedures and storage.

As a part of our disaster plan, transaction logs are backed up daily and full back ups are performed weekly on all databases. Additionally, database objects are scripted upon creation and when edited, thereby providing fast system recovery to any SQL Server.

Clinical Environment:

The Pediatric Intensive Care Unit at Children's Hospital of Pittsburgh is a 36 bed state-of the-the art multidisciplinary unit that cares for critically ill children from western Pennsylvania, West Virginia and Ohio as well as children referred from across and outside the US. More than 3,000 children are admitted to the PICU each year. The PICU team also serves as the medical command for the hospital's transport team, overseeing the rapid transport of approximately 1,500 patients annually Located on the 5th floor of UPMC's Children's Hospital, the PICU specializes in patients with:

- Severe acute respiratory distress syndrome (ARDS) and respiratory failure requiring non-conventional ventilation.
- Life-threatening cardiopulmonary failure requiring extracorporeal membrane oxygenation (ECMO)
- Trauma
- Severe sepsis and development of multi-organ system failure
- The need for continuous renal replacement therapy
- Care needs following complex thoracic, abdominal, ENT, plastic, orthopedic and neurosurgery procedures.
- Care needs in the pre- and post-transplantation setting, including liver and small bowel transplantation.

Office: Critical Care Medicine, Faculty Pavilion, Children's Hospital of Pittsburgh

Offices for faculty and support personnel are located in a dedicated research area within the Dept. of Critical Care Medicine on the 2nd floor of the Faculty Pavilion. Project management and data management and analysis will be performed in this dedicated research space, which includes a communal meeting space and two workrooms equipped with computers, an LCD projector, and networking capabilities. The servers are password-protected, and security measures are employed to maintain limited access and thus, confidentiality for maintenance of large dataset.

Computer: The PI has a personal computer in his office. The research group at the University of Pittsburgh receives dedicated support from the Information Services Division (IS) of the Department of Critical Care Medicine at the University of Pittsburgh. The IS group maintains an intranet server that will be used to facilitate

communications between all members of the research team. IS will also assist the group in connecting data retrieval and data analysis workstations to the Intranet for rapid dissemination of data to all qualified members of the research team.

(13) UNIVERSITY OF UTAH HEALTH

Scientific Environment:

The University of Utah Health Sciences (UUHS) anchors allied health science graduate schools including the College of Medicine, College of Nursing, College of Health, School of Dentistry and College of Pharmacy. Adjacent buildings include the Eccles Institute of Human Genetics, the Nora Eccles Harrison Cardiovascular Research and Training Institute, the Huntsman Cancer Institute (HCI), and Intermountain Healthcare's (Intermountain) Primary Children's Hospital (PCH) and the Eccles Primary Children's Outpatient Services Building (EPCOSB). The well-established collaborations between Intermountain and PCH with key University of Utah departments and programs enable faculty to design and successfully complete innovative research that exceeds what could be accomplished by either institution alone. University of Utah faculty members provide physician services to Intermountain and PCH, including all fetal cardiology, adult congenital heart disease, pediatric cardiology, intensive care, and cardiothoracic surgery services.

In addition to education and the multitude of avenues and services that UUHS provides, faculty and staff conduct, collaborate and initiate research aimed at advancing knowledge through innovative basic, translational, and clinical science that translate discoveries into applications that improve health. The research environment at the University of Utah is structured around multi-user core facilities. These cores offer state-of-the-art equipment and highly specialized technical services. The University of Utah is ranked among the top 30 public research universities in the nation with particular distinctions in medicine and genetics. As a result of their benchmarking research, the University received over \$309 million in research and student aid funding from external sources and ranks 15th in the nation for significant awards to faculty for research efforts.

The Pediatrics Research Enterprise includes basic science, clinical, translational, and population research organized under the Pediatric Clinical Trials Office (CTO); Translational and Comparative Effectiveness Research Scholars Program; Immunization Protection in Child Care (IPiCC); Intermountain Injury Control Research Center (IICRC); Utah Pediatric Partnership to Improve Healthcare Quality (UPIQ); and the Women and Child Institute (WCI), established as a collaboration with the Department of Obstetrics & Gynecology. These programs contain investigators skilled in conducting high level, multidisciplinary, collaborative clinical research who are available to assist in study conduct, identify barriers to accomplishing the study goals, and suggest strategies to overcome the barriers.

The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah provides data coordination and management services for a variety of national research networks. Anchoring these services is a state-of-the-art, energy efficient data center. The data center facility supports more than 3500 users around the country and provides a secure, reliable, enterprise-wide infrastructure for delivering mission critical DCC systems and services. The data center was built using high industry standards and has enhanced security to safeguard the equipment and the data within it. Security guards are on-site conducting access control 24/7/365. The data center has state of the art firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Centralized authentication and communication over public networks are encrypted using transport layer security (TLS) or virtual private network (VPN) technologies, both of which provide at least 128-bit encryption. Direct access to data center machines is only available while physically located inside our offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified of intrusion alerts. All files are protected at user/group levels; database security is handled in a similar manner with group-level access to databases, tables, and views in Microsoft SQL Server. Finally, all laptop computers in use in the DCC/division are whole-disk encrypted. The data center uses control center tools to continuously monitor systems and failure alerts. Environmental and network systems are also monitored to ensure uptime. Highly trained system administrators on staff are available to respond to high-risk emergency events. All personnel involved with data coordinating centers have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. We require all users to sign specific

agreements concerning security, confidentiality, and use of our information systems before access is provided. Data will be stored in REDCap a HIPPA compliant, secure web platform for building and managing online databases and surveys. REDCap's streamlined process for rapidly creating and designing projects offers a vast array of tools that can be tailored to our data collection strategy. The automated export procedures allow seamless data downloads to Excel and common statistical packages (SPSS, SAS, Stata, R). The platform has a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields.

The **University of Utah Department of Population Health Sciences (DPHS)** provides methodologic expertise and infrastructure that advances capacity for population health scientists to pursue impact-driven research and allows clinical professionals to provide better patient and population-oriented care. The Department provides a vibrant research environment that facilitates research and encourages support and collaboration among investigators both within the department and across health sciences. Investigators have the necessary facilities and resources to successfully implement the proposed project. Resources include ample office space and computing facilities, biostatistics support, grants and contracts administration, and scientific and career development mentoring support. Frequent seminars and chalktalks provide opportunities for study design and implementation feedback. The **Division of Health System Innovation & Research (HSIR)** in the Department of Population Health Sciences promotes the right care for every patient by enhancing the efficiency, value, and quality of care delivered by health care systems and clinicians. HSIR works within the University of Utah Health System to create a virtuous learning cycle that enables collaborators to develop and evaluate innovations that improve the quality of patient and population-orientated care. HSIR partners with community, clinical, and academic stakeholders to facilitate the implementation and dissemination of these unique developments in order to effect change to health systems and the delivery of care worldwide.

The **Genetic Science Learning Center (GSLC)** is a nationally and internationally recognized outreach and community engagement program whose mission is "making science and health easy for everyone to understand". The educational materials the Center produces are primarily disseminated via its award-winning Learn.Genetics and Teach.Genetics websites. These two sites constitute the most widely used online genetics education resource in the world and probably the most widely used online life science resource. Together, the sites receive over 18 million visits and 47 million page views annually from virtually every country in the world. The GSLC research and evaluation team uses both quantitative and qualitative methods to study the effectiveness of community educational materials and programs. The GSLC has a multidisciplinary team including experts in science/health education and educational materials development; instructional design; science/health writing; multimedia art and animation; video/movie script-writing, direction, and production; graphic design; web development; software development and programming for multiple platforms and formats, including the web and touchpad devices; music composition and audio production; bioscience research; community engagement and community-based participatory approaches; and science and health education research and program evaluation.

The **University of Utah Clinical and Translational Science Institute (CTSI)** has been continuously funded since 1965 by the NIH National Center for Research Resources (M01RR00064). The CTSI is co-directed by Drs. Rachel Hess (Contact PI) and Jennifer Majersik (PI) (UM1TR004409). The CTSI is the home for clinical and translational science at the University of Utah, the state of Utah, and within the Mountain West Region. It builds on the nationally-recognized strengths in genetics and bioinformatics to translate promising bench science into practices that improve human health. The center serves as an academic home for clinical and translational research, developing innovative health services for the community and health researchers, and training a new generation of clinical and translational investigators. Four foundations of discovery compose the center: Clinical Trials Support, Population Health, Precision Medicine, and Workforce Development, and these foundations provide support for T1 to T4 research.

The **Study Design and Biostatistics Center (SDBC)**, also co-directed by Drs. Tom Greene and Angela Presson, provides expert collaborations on study design, statistical analysis, and interpretation of results to support clinical and translational research. The SDBC is comprised of approximately 30 biostatisticians and epidemiologists and provides biostatistical support for more than 500 projects each year. The SDBC also develops novel statistical techniques and software for biomedical research. The membership of the SDBC specializes in a wide range of biostatistical areas including the design of clinical trials and observational studies,

longitudinal analysis, linear and nonlinear mixed models, survival analysis, multivariate methods, modern causal inference, methods for patient-centered research, Bayesian modeling, statistical genetics and genomics, computational statistics, and diagnostic testing. SDBC members collaborate throughout the research process, assisting with clarification of research hypotheses and study aims, optimizing study design and outcome measurements, providing sample size/power calculations and statistical analysis plans, conducting statistical analyses, interpreting analysis results, grant writing, and scientific manuscripts.

The **Qualitative, Survey and Measurement Core (QSM)** was created to aid investigators in collecting and analyzing open-ended data. QSM has an extensive track record in organizing, managing, and analyzing qualitative and survey data for NIH and PCORI funded research projects. and is housed in the University CCTS in the Medical campus, close to all major hospitals and faculty research centers. For this project, QSM will provide resources and expertise central to the qualitative work proposed in this study. QSM resources include, but are not limited to: (1) PhD trained qualitative researchers, including Dr. Zickmund, as well as (2) trained coders, transcribers, interviewers, and focus group moderators, including those who will be used and supervised for this project.

The **CCTS Clinical Trials Support (CTS)** Foundation provides assistance to investigators in the design, planning, budgeting, and performance of human subject research, including venues that can support the most complex and intensive inpatient and outpatient protocols. Their reputation for excellence in clinical research began as the University of Utah General Clinical Research Center or GCRC, an academic home for “first in human” research performance that has been generously supported by the National Institutes of Health and the University of Utah since 1984. All studies adhere to NIH policies regarding the inclusion of women, minorities, and children. The primary goals of CTS are participant safety, education, and comfort during their research visit and they take great pride in the remarkable level of satisfaction their participants describe for their CSC research experience.

Clinical Environment:

Primary Children’s Hospital (PCH), an Intermountain Health hospital, is a state-of-the-art, 289-bed, tertiary care facility, equipped and staffed to treat children with complex illness and injury. PCH is the only children’s hospital in the Intermountain West region. The catchment area spans 400,000 square miles, covering six states – Utah, Idaho, Wyoming, Nevada, Colorado, and Montana. PCH has 13,000 annual inpatient admissions and performs 15,000 surgical procedures annually. Located on the University of Utah campus, PCH has over 70 hospital services and clinics. PCH is staffed by University of Utah faculty members, integrating child health programs, research and training. Additionally, PCH serves as the base for pediatric training for the University’s Department of Pediatrics. Dr. Sweney’s primary clinical responsibilities occur in the PCH Pediatric Intensive Care Unit (PICU), a 28-bed medical-surgical ICU with 2,200 annual admissions. Dr. Sweney supervises a team of medical students, residents, fellows, and nurse practitioners to care for medically and surgically complex critically ill children, many of whom have sepsis. The other inpatient pediatric units at PCH include a 16-bed cardiac intensive care unit (CICU), a general medical unit, a neurotrauma unit, a general surgical unit, a cardiac care unit, a cancer/transplant unit, and a short-stay observation unit. In addition to these, PCH has a 50-bed level IV Neonatal Intensive Care Unit (NICU), and a dedicated Pediatric Emergency Department that is a designated Level I trauma center, and has an annual volume of approximately 40,000 visits.

IHC Health Services, Inc., (Intermountain Healthcare) is a not-for-profit health system based in Salt Lake City, Utah, with 24 hospitals (includes "virtual" hospital), 160 clinics, a Medical Group with over 2,400 physicians and advanced practice clinicians, a broad range of medical services, and a health plans division called SelectHealth. Intermountain is the largest healthcare provider in the Intermountain West, with >38,000 employees serving the healthcare needs of Utah and southeastern Idaho residents. Intermountain provided care for 1.6 million unique patients in 2018. Intermountain integrates high-quality clinical care, pioneering informatics support with reliable, deep, and broad electronic datasets, and an unparalleled commitment to supporting clinical research.

Intermountain has a long and distinguished history of leading and supporting cutting-edge clinical research from as early as the 1950s when investigators at the flagship LDS Hospital conducted formal, structured biomedical research studies. Since then, Intermountain Medical Center, PCH, three additional major tertiary teaching hospitals, 18 community hospitals, and nearly 200 community-based outpatient clinics advance the healing professions’ shared biomedical knowledge. Intermountain has participated in thousands of studies across dozens of clinical specialties. Currently,>1,500 studies are actively underway within the Intermountain system.

As part of their commitment to value in clinical practice, Intermountain invested very heavily in clinical data systems and management structures to assure they provide their patients “the best medical result at the lowest necessary cost.” The resulting data infrastructure means that every patient treated at any Intermountain inpatient or outpatient facility contributes structured data for formal learning. Intermountain stands as an example of a “Learning Healthcare System,” where routine state-of-the-art patient care also produces rapid advances in formal medical knowledge. Intermountain has previous experience implementing system-wide, evidence-based clinical programs including the management of febrile infants,⁷⁶ antibiotic stewardship,⁷⁷ diabetes prevention,⁷⁸ and decreasing elective deliveries before 39 weeks gestation.⁸⁶

Intermountain’s Healthcare Delivery Institute (HDI) was founded in 1990 with the directive of improving quality and reducing the cost of healthcare services by providing technical support and education for clinical research and process management within Intermountain. The Institute aims to improve quality and reduce the cost of healthcare services by delivering education, providing technical support, generating/disseminating evidence, and conducting research in support of operational and service excellence and process management across the Intermountain system and with external partners. Strategic priorities regarding healthcare delivery, clinical epidemiology, and health services/outcomes research are recommended based on community, clinician, and administrative needs and supported by the Institute leadership. Resources at the Institute provide data, statistical analyses, multidisciplinary research design, dissemination, and coordination to internal and external healthcare delivery and clinical research efforts that advance Intermountain’s strategic goals and attainment of mission-critical objectives. The IH Healthcare Delivery Institute is facile with the Consolidated Framework for Implementation Research, leveraging it multiple times for implementation of evidence based interventions.

The Intermountain **Enterprise Data Warehouse (EDW)** contains data capturing >20 years of patient care experience with volumes increasing steadily over time to 8.3 million encounters in 2018 alone. The repository captures clinical, administrative, financial, and claims eligibility data from 24 Intermountain hospitals and >160 outpatient clinics. Data are included from the enterprise master patient index, hospital and ambulatory case mix, clinical data repository, medical records, accounts receivable, SelectHealth claims, laboratory, pharmacy, radiology, surgery, and the emergency department. Historically, the EDW’s development focused on acquisition of new data sources and the creation of data marts and registries for specific diseases or patient populations. The EDW itself has been recognized as a key contributor to Intermountain’s role as a leading healthcare innovator in the United States.

Care Transformation/Information Services (CTIS) is a world-class research facility dedicated to the discovery and implementation of innovative information technologies for the improvement of clinical care. CTIS is focused on the pursuit of excellence in research, education, and collaboration in the medical informatics field and translates data, analytics, informatics, and medical model development into improved healthcare for Intermountain. CTIS provides Intermountain with a specific location where clinicians can direct their research questions and obtain data and analytics regarding feasibility, study design and selection of meaningful outcome measures. Together with the Office of Research, the informatics researchers in CTIS are at the forefront of Institutional Review Board (IRB)-approved patient studies at Intermountain. Through applied research, CTIS improves best-practice care by developing information system tools and advanced technologies. CTIS is considered one of the eminent Medical Informatics Centers in the world. CTIS’ vision is to leverage data, analytics, research, and commercial partnerships to accelerate the improvements of care at Intermountain. CTIS champions clinical system development and pushes the limits of technologies and care through research and clinical collaboration. Specific to this project, their expertise will be used to develop image review platforms. The system proposed for image review (Tricefy™ Imaging) for this project has been vetted by the CTIS team at PCH and is already fully integrated for research purposes.

The Learning Network at Intermountain is innovative in learning structure and opportunities, sharing best practices across the system, transforming education from passive and mandatory to sought after and interactive. The Learning Network develops and implements meaningful learning experiences for caregivers and patients. It coordinates systemwide programs and services and supports the professional development of learning experts. The Patient and Provider Publications (PPP) team works with clinical programs, services, and teams to create materials for both patients and providers that meet Intermountain best practice. For provider materials, the PPP assists clinical partners in the development of new care process models (CPMs) and clinical guidelines (CGLs) as well as best-practice flash cards and other provider-facing tools. In addition, PPP works with teams to facilitate regular reviews and updates of provider materials. The PPP offers less-costly, more efficient processes for meeting program and board goals, greater capacity to support content development and implementation with available PPP resources and more upfront, best-practice consensus. Patient education at

Intermountain is evolving to meet system priorities and changes in healthcare. The goal is to make patient education more efficient, consistent, accessible, and effective for everyone. To support patient engagement, Intermountain is working to ensure that content is **consistent** across the system and aligns with the **5 Rights of Patient Education** (right results, right person, right content, right way, right time and place). Patient education at Intermountain includes materials that are reviewed and approved by Learning Network clinical leaders and subject matter experts for system-wide use.

The Intermountain Healthcare Simulation Center is a 10,000 square foot training facility headquartered at LDS Hospital in Salt Lake City. There are 10 additional labs spread throughout Utah and southern Idaho serving 33,000 clinical and non-clinical employees, 22 hospitals and six regions spanning 84,899 square miles. Through advanced simulation technology, the simulation center provides training to thousands of hospital, homecare, and clinical professionals every year. The purpose of the Intermountain Simulation Program is to provide innovative and evidence-based healthcare services through the use of simulation technology and learning principles. Simulation learning programs are meant to promote patient safety by helping clinicians prevent errors and perform more effectively. This is done by using robotic mannequins that mimic health conditions and respond to diagnostic and treatment methods. Coupled with video recording and a live-feed conference room, training methods allows healthcare professionals to practice in a low-risk environment under close supervision. The Simulation Program provides realistic simulation training to engage learners in an atmosphere consistent with current adult learning theories. The Simulation Center currently offers a variety of training courses which all include principles from the Intermountain Healing Commitments, Crisis Resource Management, and Zero Harm. The Simulation Executive Council (SEC) drives the Intermountain Simulation strategic initiatives through recommending and approving simulation best practices. The SEC will monitor and evaluate the overall success of simulation education and patient safety initiative success. For this project, the Simulation Center houses the female mannequins and Ultrasound Mentor™ platform required for the simulation trainings on obstetric ultrasound imaging. The add on belly model and obstetric specific training modules were purchased for the pilot study.

PICU: The 48-bed Level III NICU provides care for critically ill newborns, with gestational ages ranging from approximately 22 weeks to over 40 weeks. The unique layout of the unit allows for passage of the neonate from the delivery room directly into the NICU for resuscitation to occur in the unit. This is a high-volume delivery center with a robust maternal-fetal-medicine program and high-risk delivery service. It serves as a referral center for high-risk maternal and neonatal transports, with over 600 NICU admissions annually. Infants known prenatally to require subspecialty care at Primary Children's Hospital are delivered at the University of Utah NICU and transferred to PCH by our transport team via the connecting enclosed walkway following resuscitation and stabilization. The NICU utilizes both conventional and high-frequency ventilation (HFOV and HFJV), total body cooling, inhaled nitric oxide (iNO) and subspecialty consultations from Primary Children's Hospital. Additionally, there is special expertise in the care of the extremely-low-birth-weight infants. First-year pediatric interns rotate through this NICU, allowing for ample teaching opportunities.

Office/Computer: Key study personnel have offices at the University of Utah and Intermountain campuses. Dr. Sweney is a faculty member in the Division of Pediatric Critical Care in the Department of Pediatrics at the University of Utah. The department's main administrative offices, including Dr. Sweney's private office, is located in the Williams building, centrally located on the University of Utah Research Park campus, which is within walking distance (15 minutes) to the University of Utah Health campus and Primary Children's Hospital. The Williams building is secure during business and non-business hours with electronic key entry only. Building entry and exits are monitored 24 hours per day. Dr. Sweney's office includes adequate locked file storage and shelf space.

Dr. Sweney and the research coordinators are equipped with a personal computer, large external monitor and accessories. Per University of Utah policy, all laptops and removable drives are encrypted.

(14) VIRGINIA COMMONWEALTH UNIVERSITY (VCU)

Scientific Environment:

Virginia Commonwealth University (VCU) is a degree-granting public institution located on two urban campuses in Richmond, Virginia (population 226,604) that has an annual enrollment of approximately 30,000. VCU is

categorized as a Carnegie Doctoral: Highest Research Activity, the highest ranking afforded by the Foundation. In 2011, The Carnegie Foundation elevated VCU to “Very High Research Activity” status, which combined with its “Community Engaged” designation makes VCU just one of 28 public universities in the country with academic medical centers to achieve both distinctions. VCU is one of 28 public institutions in the country that is both an NCI-designated center and has an NIH Clinical and Translational Science Award. VCU ended fiscal year 2022 with an institutional record of \$405.6 million in sponsored awards with the majority (\$176.6 million) coming from federal sources. The VCU Schools of Medicine, Nursing, Pharmacy, Dentistry, Health Sciences, and Allied Health Professionals are located on the University’s Medical College of Virginia (MCV) Campus and accounted for >50% of VCU’s total research awards, with the School of Medicine bringing in \$205.4 million alone.

VCU School of Medicine: The School of Medicine has over 5,000 networked desktop/laptop computers (minimum configurations are 2GHz Pentium 4 system with 1 GB of RAM running Windows XP Service Pack 3) that run an array of software. Our current network topology uses Ethernet technology, 100 megabits per second, to optimize speed of transfer within the LAN and high speed, and Wireless broadband service outside of the LAN. The server profile for the School of Medicine features 14 virtual and physical servers, including two file servers with 14+TB disk storage running on Active Directory as well as three additional storage area networks and a newly purchased network attached storage solution for research core facilities. The VCU Pediatrics Department has access to the VCU local area and wireless networks and receives support from the School of Medicine Technology Services Infrastructure and Client Services group, which is comprised of a team of over 20 individuals.

VCU's Wright Center for Clinical Translational Research (CCTR): In 2010, the National Institutes of Health awarded VCU with a \$20 million Clinical and Translational Science Award to integrate the Wright Center with a national consortium of more than 60 research institutions funded through the National Center for Advancing Translational Sciences. This funding was competitively renewed in 2023 for just under \$28 million over the next seven years. As the first academic health center in Virginia to receive a CTSA, VCU belongs to a national network of research institutions that are working to accelerate the transformation of laboratory discoveries into treatments for patients, engage communities in clinical research and train a new generation of clinical and translational scholars. The Wright Center provides relevant, ongoing and meaningful support to researchers in critical areas such as: access to the Trial Innovation Network (TIN); Biostatistical support; Community Engagement; consultations with senior subject matter experts; internally competed and external funding opportunities; Study Participation and Recruitment assistance; and research navigation.

Child Health Research Institute: The Child Health Research Institute is a joint initiative of the Children's Hospital of Richmond and Virginia Commonwealth University. It was launched in February 2020 with a \$2.17 million dollar grant from the Children's Hospital Foundation. The Institute is focused around four themes - Translational and Personalized Medicine, Neurosciences, Health Equity, and Emergency/Intensive Care/Cardiopulmonary Science. Since launching, it has internally competed and distributed over \$750,000 in grant support for early-stage seed grants and for cross-disciplinary collaborations that relate to children's health. It sponsors an annual conference, a visiting professor program, and provides statistical and, grant-writing support and pre- and post-award grant management support for researchers working in these thematic areas. Members of the Department of Pediatrics/Child Health Research Institute are involved in 104 research projects ranging from bench to translational and from epidemiological to service delivery, with an annual research budget of just under \$6,000,000.

Clinical Environment:

VCU Health System and Children's Hospital of Richmond (CHoR) : VCU Medical Center is the only academic medical center in Central Virginia and one of the leading centers nationwide; it is a top ranked hospital in Virginia. VCU Medical Center includes the region's only Level I trauma center, VCU Massey Cancer Center (the first NCI-designated cancer center in Virginia), 822 inpatient beds, outpatient clinics, and the VCU Health Sciences Schools of Allied Health Professions, Dentistry, Medicine, Pharmacy and Nursing. Its 600 physician/faculty members offer state-of-the-art care in more than 200 specialty areas. VCU Medical Center records over 34,105 admissions and more than 580,005 outpatient visits each year and is the largest single provider of indigent care in the Commonwealth of Virginia. CHoR at VCU is VCU's premier pediatric outpatient building which opened in 2016. CHoR boasts 643,000 ft² of clinical, research and support space, including the Pediatric Research Unit which includes a full-time dedicated clinical research nurse, scheduling, logistical support and space for

participant study visits enrolled in clinical research, all within the same building as their clinical appointments. CHoR is Virginia's only Level 1 pediatric trauma center and offers a wide range of children's health services, including pediatric emergency services, primary care, specialty and subspecialty care, burn, trauma, transplant and long-term care. With more than 15 locations across Central Virginia, CHoR provides pediatric inpatient and outpatient services that cover nearly all children's health-related needs. As part of the VCU Medical Center, CHoR is committed to ensuring access to care for all children, training future pediatric caregivers and making new discoveries that improve understanding and treatment of childhood diseases. CHoR is an Institutional Member (voting) of the Children's Hospital Association; serving as the primary teaching site of an organized pediatric department of an approved medical school.

In April of 2023, CHoR added a \$400 million, 500,000 sq ft free-standing children's hospital. The inpatient building includes 86 private inpatient beds, 16 stories of clinical and support space, new operating rooms, imaging capacity, and an emergency department all dedicated to serving the health needs of children and the community. CHoR at VCU has been repeatedly recognized as one of the Best Children's Hospitals by U.S. News and World Report (USNWR) and in 2022, was ranked in the nation's top 50 children's hospitals in eight out of ten pediatric specialties including: Nephrology #26, Pulmonology #26, Gastroenterology #36, and Cancer #37.

VCU Investigational Pharmacy

The investigational pharmacy provides the support needed to ensure safe and efficient conduct of clinical drug trials. Utilization of the IDS for investigational drug control aids researchers in protecting human research subjects through improved drug security, safety and accountability. The IDS has extension experience in complying with government regulations, accreditation standards of The Joint Commission and the Association of Human Research Protection Programs, and institutional policies for investigational drug control.

Office: Pediatric department faculty are provided personal office space in the Children's Pavilion on one floor which allows for ease of collaboration.

Computer: All offices include essential equipment including telephone, high-quality color printer/fax, licensed computer and monitors with access to Office Suite, statistical software programs including SAS, and high-speed internet. VCU's Information Technology department provides support services to ensure maintenance and timely upgrades of all software and hardware. Additional services include assistance in the use of university computer resources such as security, tele-conferencing, research computing (high performance computing, bioinformatics, statistical computing, database support), data storage, data archiving, and data backup and recovery services. VCU also has a satellite hot-site facility to protect data and keep mission-critical systems functioning during unplanned power outages.

VCU provides access to secure web-based database building using REDCap through its grant support UL1TR002649 from the National Center for Research Resources. The Pediatric Research Office, composed of both research administrators and clinical coordinators, supports over 50 active studies by providing comprehensive pre and post award administrative, fiscal, regulatory, and study coordination support to pediatric researchers and other aligned clinicians conducting basic or translational science as well as clinical pediatric research as part of CHoR. The clinical research staff are strategically assigned to develop a deep knowledge base in specific patient populations and disease processes in order to provide highly skilled and efficient support.

Biohazards and Biosafety

The research teams follow a comprehensive biosafety program and are committed to providing a safe and secure research laboratory environment that is fully compliant with all applicable federal, state and local regulations. The Safety Director and the Safety Committee are responsible for developing, maintaining and monitoring the effectiveness of their institution's program.

Safety Training:

All new hires must complete safety training before working in the laboratory. Training is tailored to each worker's assigned responsibilities and includes a combination of didactic and hands-on activities. In addition, each new worker is assigned an experienced mentor who reinforces the required work practices while directly supervising the worker. Examples of subject matter and tasks covered during training include agent-specific hazards, bloodborne pathogens, BSL2, proper use and care of personal protective equipment, sharps handling, spill response procedures, and exposure response.

Occupational Medicine:

All laboratory personnel must complete a baseline health screening through Environmental Health and Safety Office (EHS). The relevant Safety Director provides a detailed description of each worker's exposure risk so an appropriate screening can be done. All workers with a risk of exposure to human specimens are offered the hepatitis B vaccine, in full accordance with the OSHA Bloodborne Pathogens Standard (29 CFR 1910.1030). The completion of EHS screening is documented in each employee's file, which is maintained and monitored by the relevant Safety Director.

EQUIPMENT

NO APPLICABLE

CLINICAL RESEARCH CAPABILITIES

All participating clinical sites are part of the **Collaborative Pediatric Critical Care Research Network (CPCCRN)**, a multicenter program devoted to the investigation of the safety and efficacy of treatment management strategies used for the care of critically ill and injured children. Established in 2004, the CPCCRN network is currently made up of 12 core clinical sites and 12 ancillary sites (hospitals) and a data coordinating center (DCC).

Since its inception in 2005, the CPCCRN network has completed 32 studies/trials. Below are planned and actual enrollments for CPCCRN studies over the past three years. **Data below are provided for current CPCCRN network sites participating in OPTICOM for the studies listed.** **The overall population enrolled includes enrollment at these and other sites in the network.

The CPCCRN network brings many resources available to conduct large, multi-site clinical trials to include: existing network of clinical Sites (**See LOS and Facilities**) an established Data Coordinating Center (DCC) that offers comprehensive clinical data management services beginning at protocol development and carried through to study closeout; experience in working cooperatively with the NIH HEAL initiative, HEAL study teams and partners; extensive software resources available to support managing data and communications; and experienced Biostatisticians and data analysis.

Trial Name	Description	Funding Source	Participating Sites				Planned Enrollment	Actual Enrollment					
Acute Respiratory Distress Syndrome (ARDS)	ARDS is a prospective longitudinal observational cohort study that attempts to characterize prognostic and predictive biomarkers and provide a link between these biomarkers and the development of clinically relevant clinical outcomes.	NICHD	Children's National Hospital				NA	16					
			Children's Hospital of Philadelphia				NA	19					
			Children's Hospital of Michigan				NA	11					
			Children's Hospital of Pittsburg				NA	7					
			Nationwide Children's Hospital				NA	24					
Overall Population Enrolled			Not Hispanic		Hispanic		Unknown		Total				
			Race	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Total
			American Indian or Alaska Native	2	1	0	0	0	0	0	0	0	3
			Asian	5	4	0	0	0	0	0	0	0	9
			Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
			Black or African American	9	9	0	0	1	0	0	0	0	19
			White	14	37	0	4	6	0	1	0	0	62
			More than one Race	4	2	0	0	0	0	0	0	0	6
			Unknown or Not reported	2	3	0	5	10	0	2	2	0	24
			Total	36	56	0	9	17	0	3	2	0	123
CPCCRN Central Biorepository (CPCCRN-CB)	The purpose of this study is to collect biological samples from subjects enrolled in consented Collaborative Pediatric Critical Care Research Network (CPCCRN) studies for use in a central biorepository. The samples will include plasma for potential biomarker work and cells for DNA for future genetic inquiry.	NICHD	Children's National Hospital				NA	13					
			Children's Hospital of Philadelphia				NA	32					
			Children's Hospital of Michigan				NA	2					
			Children's Hospital of Pittsburg				NA	0					
			Nationwide Children's Hospital				NA	24					
Overall Population Enrolled			Not Hispanic		Hispanic		Unknown		Total				
			Race	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Total
			American Indian or Alaska Native	2	1	0	0	0	0	0	0	0	3
			Asian	2	1	0	0	0	0	0	0	0	3
			Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
			Black or African American	3	11	0	1	0	0	0	1	0	16
			White	20	30	0	2	10	0	0	0	0	62
			More than one Race	3	1	0	0	0	0	0	0	0	4
			Unknown or Not reported	1	3	0	4	4	0	1	0	0	13
			Total	31	47	0	7	14	0	1	1	0	101
GRACE-1	GRACE-1 is an open-label multi-center interventional trial to identify an adequate dose of GM-CSF in two different routes of delivery in children's with sepsis-induced MODS, with reversal of immunoparalysis as the primary outcome variable.	NICHD	Children's National Hospital				NA	4					
			Children's Hospital of Philadelphia				NA	16					
			Children's Hospital of Michigan				NA	9					
			Children's Hospital of Pittsburg				NA	7					
			Nationwide Children's Hospital				NA	23					
Overall Population Enrolled			Not Hispanic		Hispanic		Unknown		Total				
			Race	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Total
			American Indian or Alaska Native	0	1	0	0	1	0	0	0	0	2
			Asian	2	2	0	0	0	0	0	0	0	4
			Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
			Black or African American	6	7	0	0	0	0	0	0	0	13
			White	22	20	0	1	3	0	0	0	0	46
			More than one Race	2	1	0	0	0	0	0	0	0	3
			Unknown or Not reported	0	2	0	2	3	0	0	0	0	7
			Total	32	33	0	3	7	0	0	0	0	75

DATA COORDINATING CENTER (DCC) CAPABILITIES

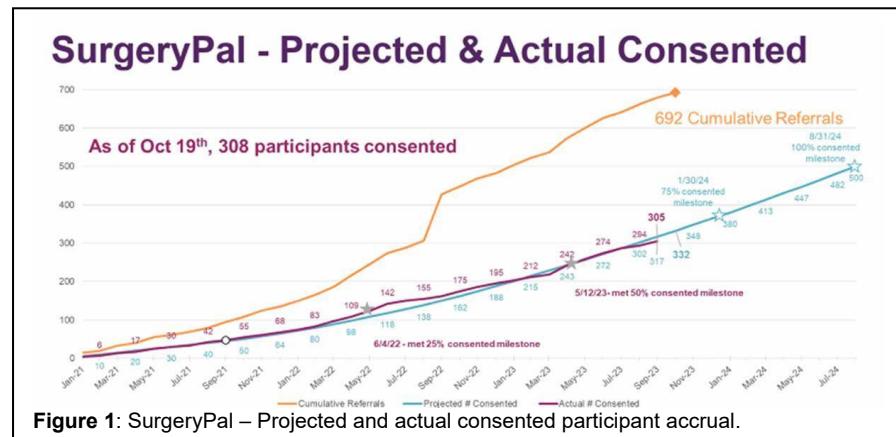
Evidence of successful past performance as a DCC for a large-scale multi-site clinical trial, preferably in pediatrics

The Data Coordinating Center at Utah University acts as the Data Coordinating Resource Center (DCRC) for all HEAL Pain Management Effectiveness Research Network (ERN) studies and handles data management activities. SurgeryPAL is example of a successful pediatric study currently underway that is a randomized controlled trial to test effectiveness of the SurgeryPal intervention (mHealth psychosocial application) vs. education control to improve acute and chronic pain and health outcomes in 500 youth undergoing major musculoskeletal surgery. Youth are randomized on an individual level using a factorial design to SurgeryPal or Education during 2 phases of intervention: 1) pre-operative phase (4 week duration delivered over the 4 weeks leading up to surgery), and 2) post-operative phase (4 week duration between weeks 2 and 6 following surgery). There are 4 treatment arms. Participants undergo 4 assessments, independent of their treatment assignment: T1: Baseline (pre-randomization); T2: acute post-surgery outcomes (daily assessment of acute outcomes beginning day 1 through day 14 after hospital discharge from surgery); T3: Post-surgery follow-up (assessment of chronic outcomes at 3-months post-surgery); T4: Final post-surgery follow-up (assessment of outcomes at 6-months post-surgery).

There are 37 sites sending in referrals to the lead site. Study enrollment continues with 309 participants consented (as of 25Oct2023) and is approaching the next study milestone of 75% enrollment by 30Jan2024. The initial database build at the DCRC was successful in meeting the timeline to start enrollment. To streamline the database change process, the Utah DCRC team developed a request form to support the intake process for such requests. The **Systems Modification Request Form (SMRF)** was developed as the first step in evaluating the rationale for the changes and other systems that might be affected (REDCap, OpenClinica, SharePoint, Tableau, raw and analysis datasets). In addition to being utilized as a brainstorming tool to help the study team think through the effects of the requested change, the tool also serves as a documentation resource providing an audit trail on why changes in the database were implemented. This process evaluates the merits of database change requests and avoids unintended consequences. This process allows the Resource Centers (RCs) and the study PI team to collaborate on the concept, options, and testing for each change at multiple steps in the process. In addition, the DCRC has successfully implemented an automated process of receiving a datafile from SurgeryPal study team not entered into the DCRC REDCap. The dataset is received weekly and integrated into the main database. Multiple SharePoint reports for SurgeryPAL have been created and pushed into production to support monitoring of study progress.

The Utah DCRC also supports the Johns Hopkins Statistical Coordinating Resource Center (SCRC) with DSMB preparation for all trials, specifically the closed report preparation. The DCRC is working collaboratively with the other RCs prepping for the next DSMB meeting scheduled for 13Dec2023. We also collaborated with the Study PIs to register SurgeryPAL with the HEAL Data Platform and complete the CEDAR metadata forms for the selected NICHD Repository.

Another example of a large-scale multi-site clinical trial in pediatrics is the Therapeutic Hypothermia in Cardiac Arrest Trials. The Pediatric Emergency Applied Research Network (PECARN) and the Collaborative Pediatric Critical Care Research Network (CPCCRN) worked collaboratively with the Utah DCC, under the direction of the lead investigator, Frank Moler (University of Michigan), to enroll participants into two separate clinical trials. A total of 38 children's hospital's pediatric intensive care units in the United States and Canada participated in these trials. One trial focused on out-of-hospital cardiac arrest and the other focused on inpatient cardiac arrest. These trials collectively enrolled 633 participants, where each was randomized to either hypothermia or normothermia following cardiac arrest, as indicated in Table 2. The primary outcome was survival with a good neurobehavioral outcome at 12 months of



follow-up after the child's cardiac arrest. Secondary outcomes were survival at 12 months after cardiac arrest and change in neurobehavioral function. As published in the New England Journal of Medicine, conclusions of both trials showed that therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit with respect to survival with good functional outcome at 12 months for children who survived both in-hospital and out-of-hospital cardiac arrest. Citations for these publications can be found in the Utah DCC *Facilities and Other Resources*.

Academic productivity as a DCC

The University of Utah Data Coordinating Center (DCC) was founded in 2001 and has provided data, statistical, and clinical coordinating center support for 12 national research networks (**Table 1**) and has implemented over 140 active or completed multi-center studies (**Table 2**) resulting in over 500 publications through June 2023. Of note, five of these networks focus on pediatrics (PECARN, CPCCRN, NPMSC, PCPLC, 4CYC). In addition, the DCC is one of the Resource Centers for the NIH funded HEAL ERN. Citations for many of these programs and trials can be found in the Utah *Facilities* Section.

Table 1: National research networks coordinated by the Utah DCC.

Network	Year Initiated
Pediatric Emergency Care Applied Research Network (PECARN)	2001
Collaborative Pediatric Critical Care Research Network (CPCCRN)	2005
Hydrocephalus Clinical Research Network (HCRN)	2006
The Network of Pediatric Multiple Sclerosis Centers (NPMSC)	2010
Neuromyelitis Optica Research Network	2012
Adult Hydrocephalus Clinical Research Network (AHCRN)	2013
Fetal Heart Society (FHS)	2014
Pediatric Colorectal and Pelvic Learning Consortium (PCPLC)	2016
Four Corners Youth Concussion Research Network (4CYC)	2016
Trial Innovation Network	2016
Scleroderma Foundation Research Network	2018
Helping to End Addiction Long-term Effectiveness Research Network (HEAL ERN)	2019

Table 2: Multi-center studies coordinated since 2001

Name of Study	Participants Enrolled	Current Status
PECARN Core Data Project (PCDP)	> 20 million (visits)	Completed
The Effectiveness of Oral Dexamethasone for Acute Bronchiolitis: A Multicenter, Randomized Controlled Trial (R40MC04298)	598	Completed
Hypothermia for Pediatric Cardiac Arrest Planning Grant (R21HD044955)	491	Completed
Planning Hypothermia Trial for Pediatric Cardiac Arrest (R34HD050531)	Not applicable	Completed
Childhood Head Trauma: A Neuroimaging Decision Rule (R40MC02461)	42,412	Completed
Predicting Cervical Spine Injury (CSI) in Children: A Multi-centered Case-Control Analysis	540	Completed
A Diagnosis Grouping System for Child ED Visits	Not applicable	Completed
A Clinical Decision Rule to Identify Children with Intra-abdominal Injuries	12,044	Completed
CPCCRN Core Data Project (CCDP)	249,306 (admissions)	Completed
Bereavement: Parents' Opinions on Physician Conference	56 (parents)	Completed
Development of a Quantitative Functional Status Scale (FSS) for Pediatric Patients	856	Completed
Bereavement: Prevalence and Risk Factors for Complicated Grief in Parents	261 (parents)	Completed
The Critical Illness Stress-induced Immune Suppression (CRISIS) Prevention Trial	293	Completed
Development of Research Partnerships with EMS Agencies and Descriptive Study of EMS Pediatric Population within PECARN	Not applicable	Completed (16 agencies, 514,880 individuals)

Name of Study	Participants Enrolled	Current Status
Patient Safety Procedures and Climate of Safety in Pediatric Emergency Departments	Not applicable	Completed (29,000 incidents in 19 hospitals)
Referral and Utilization Patterns for Psychiatric Related Visits to the Pediatric ED	462	Completed
Factors Associated with Quality of Care Delivered to Children in US Emergency Departments (R01HS019712)	621	Completed
Bereavement: Physician Perspectives on Post-Mortem Meetings with Parents	70 (physicians)	Completed
Cortisol Quantification Investigation: Prospective, Observational Study of Free versus Total Serum Cortisol in PICU Patients	165	Completed
Critical Pertussis in U.S. Children: Severe Morbidity, Sequelae and Mortality: A Prospective Cohort Study	225	Completed
Measuring Opioid Tolerance Induced by Fentanyl (MOTIF)	419	Completed
Qualitative and Quantitative Evaluation of Patient Safety Issues in Pediatric Emergency Departments: Pilot Study in New York State	3,281	Completed
Application of Transcriptional Signatures for Diagnosis of Febrile Infants within the PECARN Network	6,014	Completed
Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA Trials) (U01HL094345, U01HL094339)	299 out-of-hospital; 334 in-hospital	Completed
Critical Asthma in the Pediatric Intensive Care Unit	261	Completed
Phenotypes, Genomics, and Outcomes in Sepsis (POGOS) Recruitment Pilot	157	Completed
Bereavement: Pilot Study of Framework for Physician-Parent Follow-up Meetings	46 (interviews)	Completed
Trichotomous Outcome Prediction: Ideal Time Interval for Severity of Illness Assessment	376	Completed
Semantic Interoperability for CPCCRN Core Data Project	Not applicable	Completed
Hydrocephalus Clinical Research Network Pediatric Registry (RC1NS068943)	6,378	Enrolling
Ventricular Catheter Placement Study: Assessment of efficacy and safety of an ultrasound guided shunt insertion technique	119	Completed
Shunt outcomes in post-hemorrhagic hydrocephalus (SOPHH): A network pilot study	125	Enrolling
Environmental and Genetic Risk Factors for Pediatric Multiple Sclerosis (R01NS071463)	1,379	Complete
Pediatric Multiple Sclerosis and Demyelinating Diseases Registry	2,944	Enrolling
MRI Analysis of Pediatric Demyelinating Disorders: NMO Spectrum	238	Completed
RNA Biosignatures in the Emergency Evaluation of Febrile Infants (R01HD062477)	4,797	Completed
Fluid Therapy and Cerebral Injury in Pediatric Diabetic Ketoacidosis RCT (R01HD062417)	1,389	Enrollment Complete
Implementation of the PECARN Traumatic Brain Injury Prediction Rules for Children Using Computerized Clinical Decision Support: an Interrupted Time Series Trial (ARRA S02MC19289)	19,000	Completed
Teen Alcohol Screening in the Pediatric Emergency Department	5,118	Completed
Microbiomes in Pediatric Multiple Sclerosis	128	Completed
Intravenous Magnesium for Sickle Cell Vaso-occlusive Crisis RCT (R01HD062347)	208	Completed

Name of Study	Participants Enrolled	Current Status
Translating an Adult Ventilator Computer Protocol to Pediatric Critical Care (R21HD061870)	120	Completed
Trichotomous Outcome Prediction in Critical Care (TOPICC)	10,778	Completed
CPCCRN Informatics Initiative: picuGrid Project	Not applicable	Completed
Ventricular Size Involvement in Neuropsychological Outcomes in Pediatric Hydrocephalus	60	Completed
Cerebrospinal Fluid Markers of Post-Hemorrhagic Hydrocephalus	231	Completed
A Multicenter Retrospective Study of Endoscopic Third Ventriculostomy (ETV) and Choroid Plexus Cauterization (CPC) in Children with Hydrocephalus	43	Completed
Collaborative International Research in Clinical and Longitudinal Experience for Neuromyelitis Optica (NMO) Studies	1,000	Completed
Collaborative National Quality and Efficacy Scleroderma Registry	591	Enrolling
Improving the Quality of Pediatric Emergency Care Using an Electronic Health Record Registry and Clinician Feedback (R01HS020270)	Not applicable	On-going through 2016, 12 hospitals, 5.8 million visits
Prospective Yield Study of Children with Severe Traumatic Brain Injury: Pilot	298	Completed
Feasibility for a RCT of Progesterone for Severe TBI		
Planning a Multicenter Cooling Trial for Hyperammonemic Metabolic Crises (R34HD072101)	Not applicable	Completed
Bleeding and Thrombosis During ECMO - BATE	514	Completed
Age Specific Screen for Ethanol and Substance Status (R01AA021900)	5,067	Accrual completed
ED-initiated School-based Asthma Medication Supervision	16	Completed
Pediatric ECMO and Cefepime and Zosyn (PEACE(AZ))	17	Completed
Impact of Emergency Department Probiotic Treatment of Pediatric Gastroenteritis RCT (R01HD071915)	971	Enrollment Complete
Impact of Hypothermia on Midazolam and Morphine Pharmacokinetics (R01HL112745)	11	Completed
Collaborative International Research in Clinical and Longitudinal Experience for Neuromyelitis Optica (CIRCLES)	1000	Completed
Pediatric Intensive Care Quality of Cardiopulmonary Resuscitation (PICqCPR)	368	Completed
An Open-label add-on of Cetirizine for Neuromyelitis Optica	19	Enrollment complete
Life after Pediatric Sepsis Evaluation - LAPSE (R01HD073362)	392	Completed
Inflammation Phenotypes in Pediatric Sepsis Induced Multiple Organ Failure - PHENOMS (R01GM108618)	410	Enrollment complete
A Multicenter Prospective Study of Endoscopic Third Ventriculostomy (ETV) and Choroid Plexus Cauterization (CPC) in Children with Hydrocephalus (U01NS107486)	79	Enrolling
Emergency Department Screen for Teens at Risk for Suicide (ED-STARS) (U01MH104311)	10,054	Completed
A Randomized Controlled Trial of Anterior versus Posterior Entry Site for CSF Shunt Insertion (PCORI CER-1403-13857)	453	Completed
Adult Hydrocephalus Clinical Research Registry	2,003	Enrolling
Arginine Therapy for Treatment of Pain in Children with Sickle Cell Disease (Feasibility and pK Studies) (R34HL122557)	400	Accrual completed
Sepsis Induced Red Cell Dysfunction (SIRD) (R01GM113838)	175	Completed

Name of Study	Participants Enrolled	Current Status
GM-CSF for Immunomodulation following Trauma (GIFT) (R01GM094203)	117	Completed
Inhaled Nitric Oxide Use in Pediatric Intensive Care	578	Completed
Pediatric Colorectal and Pelvic Learning Consortium Registry	3,051	Enrolling
4 Corners Youth Consortium Concussion Registry	1,412	Enrolling
Prediction and Prevention of Preterm Birth: A Prospective, Randomized Intervention Trial	1,191	Completed
Development of a Pediatric Cervical Spine Injury Risk Assessment Tool (R01HD091347)	22,463	Enrolling
Headache Assessment of Children for Emergent Intracranial Abnormalities (R01NS110826)	5,695	Enrolling
Microbiome, Virome and Host Responses Preceding Ventilator-Associated Pneumonia (VAP) (R01HL124103)	512	Completed
Efficacy of DE-MRI-Guided Ablation versus Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II)	843	Completed
RNA Biosignatures: A paradigm change for the management of young febrile infants (R01HD085233)	2,612	Enrollment complete
Informing the Research Agenda for Pediatric Intensive Care Units (IRA)	328	Completed
Parent-Provider Alliance in Pediatric Intensive Care (PPA)	238 (parents)	Completed
GM-CSF for Reversal of Immunoparalysis in Pediatric Sepsis-induced MODS (GRACE)	23	Enrollment complete
Improving Outcomes from Pediatric Cardiac Arrest (ICU-RESUS) (R01HL131544, R01HL147616)	1,144	Enrollment complete
Assessment of Health-related Quality of Life and Functional Outcomes after Pediatric Trauma (TOUCH)	430	Completed
Core Outcomes Set (COS) for Pediatric Critical Care Medicine Research (PICU-COS)	30 (interviews)	Completed
Acute Respiratory Distress Syndrome (ARDS)	123	Completed
Randomized Controlled Trial of Valgancyclovir for CMV-infected Hearing Impaired Infants (U01DC014706)	10	Completed
Childhood Radiologically Isolated Syndrome	56	Enrollment complete
Impact of Socioeconomic and Geographic Factors on Prenatal Diagnosis of Hypoplastic Left Heart Syndrome and d-Transposition of the Great Arteries	2,022	Completed
Procalcitonin to Reduce Antibiotic Use in Pediatric Pneumonia (R34HL153474)	1	Completed
24 Hour Risk for Suicide Attempts in a National Cohort of Adolescents (R01MH113582)	929	Enrollment complete
Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children (R34HL135214)	31	Completed
Improving Detection of STIs in the Pediatric ED: A Pragmatic Trial (R01HD094213)	13,689	Enrollment complete
Effect of ED and after-ED Analgesic Treatment on Pediatric Long Bone Fracture Outcomes (R01HD091302)	5,783	Enrolling
Bedside Exclusion of Pulmonary Embolism in Children without Radiation (BEEPER) (R01HL148247)	2,178	Enrolling
Implementation of Evidence Based Care for the Acute Treatment of Sickle Cell	4,578 Visits in registry	Completed

Name of Study	Participants Enrolled	Current Status
Disease Pain (U01HL143477)		
Sickle Cell Improvement: Enhancing Care in the ED (U01HL159850)	1,378	Enrolling
Sickle Cell Disease Treatment with Arginine Therapy (STArT Trial) (UH3HL148560, U24HL148563)	102	Enrolling
Patient and Family Views on Pediatric Multiple Sclerosis Needs, Outcomes and Methods	198	Enrollment complete
UTAH One (Understanding Treatment and Health in the Ongoing Corona Epidemic): A Hydroxychloroquine Outpatient Study (U24TR001597)	368	Completed
Hydroxychloroquine vs. Azithromycin for Outpatients in Utah with COVID-19 (U24TR001597)	177	Completed
Chilled Platelets Study (USMRAA W81XWH-20-9-0021)	71	Enrolling
Diet and Relapses in Pediatric Multiple Sclerosis (R01NS117541)	209	Completed
Comparative Effectiveness and Complications of IV Ceftriaxone Compared with Oral Doxycycline in Lyme Meningitis (R01AI151180)	8	Enrolling
A Sequenced-Strategy for Improving Outcomes in Patients with Knee Osteoarthritis Pain (UH3AR077360)	Phase 1:437, Phase 2:402	Enrolling
Tailored Non-Pharmacotherapy Services for Chronic Pain: Testing Scalable and Pragmatic Approaches (UH3AG067493)	2,333	Enrollment complete
Effectiveness of an MHealth Psychosocial Intervention to Prevent Transition from Acute to Chronic Postsurgical Pain in Adolescents (UH3HD102038)	237	Enrolling
Integrated Treatment for Veterans with Co-Occurring Chronic Pain and Opioid Use Disorder (UH3DA051241)	98	Enrolling
Placebo Controlled Effectiveness in iNPH Shunting (PENS) Trial (U01NS122764)	1	Enrolling
Optimizing the Use of Ketamine to Reduce Chronic Post-surgical Pain (UH3CA261067)	188	Enrolling
Endophenotypes of Persistent Post-Concussive Symptoms in Adolescents: CARE4Kids (U54NS121688)	19	Enrolling
Azithromycin Therapy in Pre-schoolers with Severe Wheezing Episode (UH3HL147016, U24HL147018)	214	Enrolling
Hyperhydration to Improve Kidney Outcomes in Children with Shiga Toxin-Producing E. coli Infection (HIKO STEC) (R01AI165327)	3	Enrolling
Personalized Immunomodulation in Pediatric Sepsis-induced MODS (PL1HD105462)	141	Enrolling
Pediatric Dose Optimization for Seizures in EMS PediDOSE (U01NS114042)	59	Enrolling
An Observational Study of Skin Reaction in Infants Using the Owlet Babysat Oximeter	43	Completed
The Follow-up Automatically vs. As-Needed Comparison Trial (FAAN-C) (IHS2021-22388)	1	Enrolling
Prospective Evaluation Analysis and Kinetics of IV Sotalol (PEAKS Sotalol) (50304268)	50	Enrolling

Name of Study	Participants Enrolled	Current Status
Intravenous Magnesium: Prompt use for Asthma in Children Treated in the Emergency Department (1R34HL152047-01A1)	2	Enrolling

DCC staffing plan and capabilities

Principal Investigator: Dr. Richard Holubkov is a senior biostatistician for the OPTICOM DCC and a Professor at the University of Utah. He has been the lead biostatistician for several large research networks and multicenter trials and has nearly four decades of experience in the design, management, analysis, and reporting of data from prospective studies. These studies have included the DECAAF-II trial testing ablation treatments on subjects with atrial fibrillation, and the Artificial Valve Endocarditis Reduction Trial (AVERT) assessing thromboembolic events and other complications following heart valve replacement. In addition, Dr. Holubkov has been the senior biostatistician for the CPCCR network since its inception in 2005. Dr. Holubkov will be responsible for all aspects of the proposed OPTICOM Data Coordinating Center (DCC) activities, including ensuring that appropriate data are collected to accomplish the goals of the study. Dr. Holubkov will participate in study investigator teleconferences and project meetings, oversee development of analysis datasets, as well as provide statistical expertise for the project. Dr. Holubkov will present interim analyses at DSMB meetings, oversee final analyses, and assist in abstract and manuscript preparation.

Co-Investigator: Dr. Ron Reeder is a Biostatistician and Associate Professor of Pediatrics at the University of Utah. Dr. Reeder has supported and directed two clinical research networks and has led several multi-center clinical trials and observational studies at the Utah DCC. Along with Dr. Holubkov, Dr. Reeder will be responsible for oversight of the proposed investigation at the OPTICOM DCC. He will serve as the primary statistical contact, and he will direct the efforts of the OPTICOM DCC to provide data management and statistical support for the proposed study.

Program Director: Dr. Amy Goodman is a Director of Research & Science at the Utah DCC. She is a PhD in biomedical engineering with expertise in active implantable medical devices and neuromodulation for pain. Dr. Goodman has over 20 years of experience in clinical research leadership, both in early-stage device companies (industry) and academic medical research (University of California, San Francisco, and University of Utah). She served the Director of the NIH-funded Phase III trial evaluating erythropoietin in newborns with HIE. Dr. Goodman will oversee all OPTICOM DCC activities and the DCC budget. She will establish and ensure consistent communication with the Principal Investigators and Project Managers. She will assure that the DCC team is functioning efficiently to support the project. She will work closely with the Director of Regulatory Affairs and Quality Assurance to ensure regulatory requirements are addressed. She will ensure that team members are replaced and trained if there is a staff change at the DCC.

Project Managers: Ms. Renee Kuhn and Mr. Jordan Bridges will serve as project managers at the DCC. Ms. Kuhn has been a project manager at the DCC for over 12 years. Her previous experience includes managing the Therapeutic Hypothermia after Cardiac Arrest Trials (THAPCA Trials). Mr. Bridges has been with the DCC for four years and has a background in conducting randomized clinical trials. He currently serves as a project manager for the HEAL Effectiveness Research Network. Ms. Kuhn and Mr. Bridges will be responsible for interfacing with DCC site personnel, managing the reliance and sIRB process, tracking regulatory documents, assisting with protocol and study document development, and working with the Clinical Data Manager to assure high quality data submission. The Project Managers will develop the Manual of Operations, the protocol, and any training materials including online training as appropriate. They manage timelines, establish and complete a risk assessment document, and create a plan to mitigate risks identified. They will create the paper forms to be used for initial data collection prior to entry into the database. They will also be responsible for conducting remote monitoring activities as needed to verify data quality and provide site study training. Ms. Kuhn and Mr. Bridges will coordinate research coordinator training and will conduct teleconference calls as needed. They will help to coordinate data harmonization, curation, and sharing efforts, and project management related to efforts at Utah. They will also serve as a point of contact for study teams and DCCs and will facilitate registration of study information to the HEAL data ecosystem.

Clinical Data Manager: Mr. Volker Freimann has been with the DCC for nine years and has a background in conducting randomized clinical trials. He currently serves as a senior clinical data manager on multiple networks. Mr. Freimann will be responsible for identifying the data variables from the study protocol. He will also

develop the database plan and create the electronic data capture system that sites will use to enter the data. He will be responsible for day-to-day monitoring of data submitted from the individual sites. He will prepare regular internal and external reports concerning data quality and will work closely with the DCC Project Manager to determine areas of needed additional training at each site. He will also develop discrepancy rules that will automatically identify missing and errant data and will send nightly query notification to sites to initiate correction of data entry errors. The data manager will monitor query resolution status. He will also lock data prior to data safety monitoring board reviews, and will make any database changes, or update the database variables as necessary. He will lock the final dataset prior to study analyses.

Biostatistician: Mr. Russell Banks is a staff biostatistician at the Utah DCC. He has over eight years of experience providing statistical support for multicenter studies in pediatric critical care and emergency medicine. He earned a Master of Science in Statistics degree from Utah State University in 2015. Mr. Banks will be primarily responsible for data analysis. He will work with Drs. Holubkov and Reeder to conduct all statistical analyses. He will prepare formal data reports and provide all data safety monitoring board reports based on locked data at intervals during the trial. He will review all manuscript requests and create manuscript mapping plans for individual manuscripts as requested by the Principal Investigators (MPIs). The manuscript plans will be coded during the enrollment period and iteratively reviewed by the lead authors. Data will be checked for missingness and accuracy. He will prepare final data analysis sets and will assist with final manuscript preparation. Mr. Banks will develop a public use data set or a final de-identified dataset for sharing with the funding agency and coordinate sharing with HEAL Data Repositories.

IT Project Manager: Ms. Sally Perez is a Sr. IT Project Manager for clinical projects at the Utah DCC. Ms. Perez received her bachelor's degree in management information systems from Texas A&M University. She has over twenty years of project management experience and is a certified Project Management Professional (PMP). Ms. Perez supports numerous clinical projects in multiple networks and provides technical project management support from DCC startup through the enrollment phase. Sally is responsible for tracking and reporting the progress of projects and for highlighting risks in a continuing effort to protect the critical project timelines and milestones. Ms. Perez will ensure communication, timelines, and deliverables within the team. She will communicate with the DCC Project Manager any changes or issues that need to be discussed with the clinical team. She will attend regular team meeting to discuss needs, study progress, and development, and may attend key strategic meetings and calls.

Regulatory Affairs and Quality Assurance: Ms. Maryse Brulotte is certified as a Clinical Research Associate (CRA) and has served as the Director of Regulatory Affairs and Quality Assurance at the DCC for five years. She has a baccalaureate and post graduate degrees in pharmacy and has served as a Project Manager at Contract Research Organizations (CROs) and as a director of operations for a startup pharmaceutical company. She has broad experience managing quality, regulatory, and clinical research operations. She has developed a comprehensive Quality Management System to facilitate implementation of quality-by-design and risk-based monitoring approaches at the DCC and she oversees the development of risk-based monitoring plans for DCC studies.

Ms. Brulotte will assist the DCC project manager with completion of the risk assessment and risk management plan for the OPTICOM study. Ms. Brulotte has assisted in the preparation of many risk management plans. She has regulatory experience and continuously updates the DCC's risk plans to reflect federal and international regulations. She will assure that risks are appropriately identified and mitigated at the beginning of the study. She will also help assure that the reports that are produced by the DCC study team reflect key risks and the study outcomes. She will provide consultation on any regulations that affect the study and will assist with any required IND reporting.

Administrative Assistant: Ms. Tiffany Dubbelman has provided administrative support for multiple projects at the Utah DCC for more than 5 years and will be responsible for setting up and organizing internal DCC meetings, setting up study-specific webinars that may be recorded, organizing trial documents at the DCC in our electronic storage system, and assuring that regulatory documents are stored and easily accessible. Ms. Dubbelman will also take minutes of meetings and will assist with setting up key study meetings with investigators, sites or others as requested. Ms. Dubbelman will also be responsible for assisting with organizing training materials on our electronic learning platform as needed.

Capacity and ability to manage data and communications

The OPTICOM DCC has extensive software resources available to support managing data and communications.

Query Management System: While EDC systems such as REDCap have data field validation, sophisticated validation of data between different forms requires processing after data are submitted to the Utah DCC. We have written a Java-based application called the Query Management System and have used it successfully for 20 years to manage all queries for data discrepancies. The clinical data manager determines the business (validation) rules for each data element, and SQL queries are written to enforce each rule. The system executes during the night, identifies all new data discrepancies, and creates a single email to each site research coordinator that contains all the new discrepancies. Discrepancies are not repeated in email notification for seven days, a feature appreciated by research coordinators. Most importantly, if the data discrepancy is corrected in the EDC by the site research coordinator, the system automatically resolves the query without requiring DCC staff intervention. The Query Management System does *not* have read or write access to the EDC, and all data entry by sites is done via the EDC system. If the research coordinator needs to communicate with the clinical data manager and request manual resolution, this is also done through the system, so a complete audit trail is available for all data element changes and query resolutions.

Electronic Collaboration Support: eRoom™: The DCC has used eRoom™ to provide a “digital office” to support secure, efficient, confidential communication and collaboration among multiple users (>1200 current users) for over two decades. The software is Web-based and uses an office metaphor of rooms that may contain folders, documents, task lists, calendars, and task-oriented databases. The software is highly secure, and management of documents is intuitive.

The user can drag documents to and from their own desktop directly into the eRoom™ system. The system is optimized to integrate with standard office applications. We have used eRoom™ to support all aspects of our networks since their respective inceptions, including coordination of the Steering Committee and subcommittees, preparation of protocols, grants, manuscript preparation and publication, tracking Institutional Review Board (IRB) applications and approvals, and storage of scanned regulatory documents. eRoom™ provides significant efficiency, as it eliminates printing and mailing large paper documents. The system allows us to automatically notify study personnel of protocol changes, updates to Manuals of Operation, and important communications within any individual project. Investigator and research coordinator acceptance of eRoom™ has been enthusiastic and uniform in the > 140 multi-center studies we have coordinated.

Twilio®: We use Twilio®, a cloud communications platform, to send automated messages such as texts and email to research participants. We have used this technology to enable automated reminders and communication to participants, which encourages increased compliance with follow up data and participant retention. The technology also provides the ability to conduct remote data collection from a participant via SMS text or email.

SQL Server Database and Reporting Infrastructure: We use Microsoft SQL Server as our primary relational database management system (RDBMS) and have extensive experience (over 25 years) accessing the database from SAS, R, PHP, Perl, Python, and Java. Microsoft SQL Server provides sophisticated security facilities.

All study reports are based on data housed in the study data warehouse or study data marts, depending on the overall dataset size. A data mart is a simple, focused version of the data warehouse, and contains a repository of summarized data collected for analysis. The described architecture contributes to streamlined, efficient data processing for frequently refreshed reports.

We adopt a defense-in-depth approach to information security. All data are encrypted in-transit across communication channels using currently supported version of Transport Layer Security (TLS). Authentication, authorization, and encryption at-rest are implemented using the Windows Data Protection application programming interface (API). Data warehouses, databases, and data marts are only accessible on-premises at the Utah DCC or with an established VPN.

Clinical Data Management:

The DCC offers comprehensive clinical data management services beginning at protocol development and carried through to study closeout. The major components of our data management approach are outlined in Figure 2. We use systems and processes to adhere to the Society for Clinical Data Management's Good Clinical Data Management Practice©.

Evidence of reporting capabilities

Business Intelligence and Analytics Software:

The DCC has extensive experience producing interactive dashboards on our website for public and

government partners. As an example, The National Emergency Medical Services Information System (NEMSIS) Technical Assistance Center is hosted at the Utah DCC and facilitates, enables, and promotes the implementation and use of the National EMS Data Repository through maintaining and supporting forward-facing services and tools. These include reports, dashboards, multi-dimensional Online Analytical Processing (OLAP) cubes, annual Public-Release Research Datasets, and direct research assistance. The DCC uses Tableau, Power BI, and SQL Server Reporting Services (SSRS) for data analysis and business intelligence. By leveraging these visualization tools, we can create interactive dashboards, allowing viewers to filter datasets on variables of interest and export the data in easily consumable formats. Reports are generated for stakeholders through Tableau dashboards using repository data. The reports are refreshed with current data on an hourly, daily, or monthly basis. Users can subscribe to email push notifications from certain reports for current information delivered directly to their email. Dashboards provide an accessible way for users of all experience levels to interact with a tremendous amount of data in near real time. Access to dashboards can be restricted to specific user groups based on the data shared and who is authorized to view and utilize that level of information. We have also designed dashboards to provide review of longitudinal data trends. Informed by our experience, multiple levels of access can be provided, from public-facing, investigator, NIH, or other. Authorized users are granted permissions to reports and dashboards through layered security, which includes an approved Active Directory (AD) account and report-level permissions within the reporting tool. For a visual reference regarding Tableau, see the **DCC Facilities**.

Tableau allows for the consolidation of study data and translation of that data into information provided in real-time to authorized users involved with the multi-center study. In our research networks, we permit every investigator, research coordinator, and other research staff to access these read-only reports. Our reports include overall and site-specific performance metric reports, study demographics, and enrollment and data quality reports. The default setting for all reports displays all sites and includes the entire duration of each study. The reports are purposefully not anonymized, as we have found that transparency about site performance, for example enrollment and retention, enables the sharing of best practices from high performing sites, and the opportunity for improvement for sites performing at a lower level. An important feature of these reports is the ability for users to customize the date range and sites included in the report, which allows a site to compare its performance at different time points in a study.

Statistical Software: The DCC uses SAS Version 9.4 for most analyses, and R for specific reporting purposes. The team considers SAS to be most appropriate for trials that are subject to an investigational new

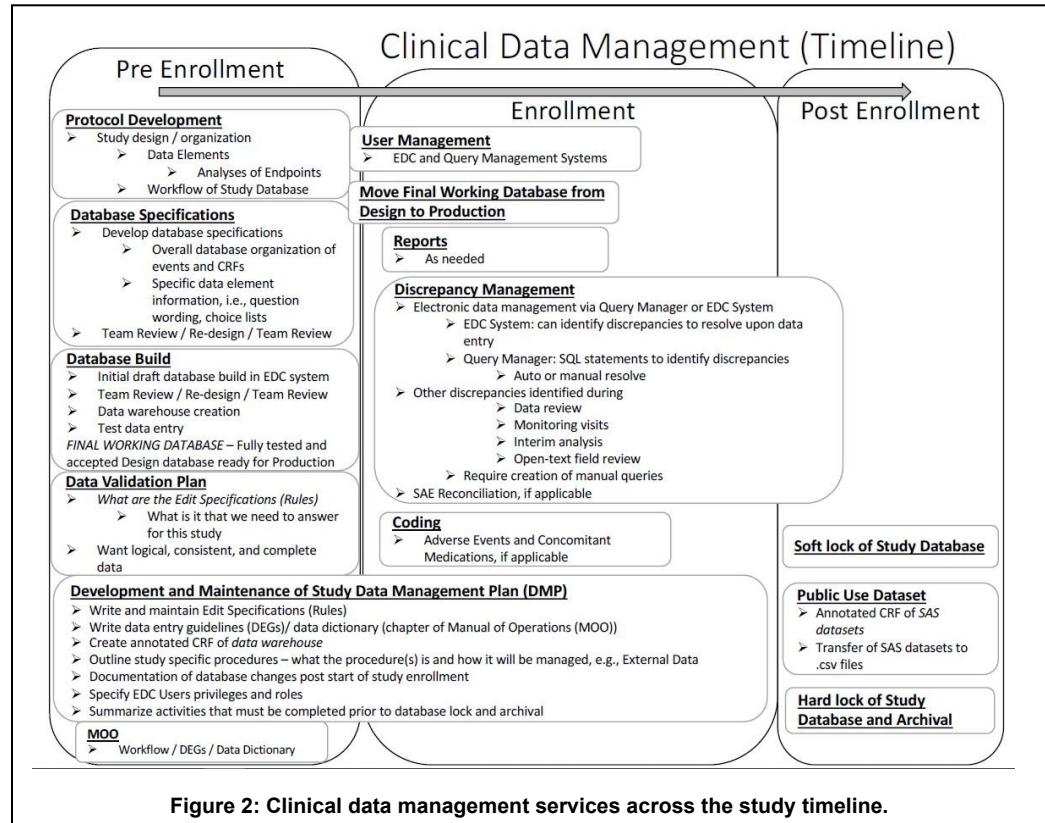


Figure 2: Clinical data management services across the study timeline.

drug (IND) application, as SAS has documentation to support its validation, while R is highly customizable by end users.

Preparation of Public-Use Datasets: To meet the NIH Data management and sharing and to facilitate data transparency and make data more publicly available and in accordance to the HEAL Data Sharing policies, the OPTCOM DCC staff create a public-use dataset (PUD) after completion of each study and publication of primary results. Project Management, Clinical Data Management, and Biostatistics staff jointly work to de-identify study data and prepare these data for sharing. We have shared multiple datasets previously for our federally funded studies.

De-identification involves randomly generating a new ID for each participant, recoding variables as needed, and removal or redaction of open text fields to remove PHI. Accompanying documentation (e.g., study protocol, annotated electronic case report forms) is updated to provide guidance to researchers that utilize the PUD. All shareable PUD materials are reviewed and approved by study investigators prior to deposit in a suitable repository. Our data sharing plan will include data type, method of sharing, data access and sharing processes. All data and metadata will be submitted to study-appropriate, **HEAL-compliant data repositories** to ensure the data is accessible via the HEAL Initiative Data Ecosystem ([see DMSP](#)).

Ability to provide on-site and off-site monitoring

The OPTCOM DCC uses both on-site and off-site monitoring. Remote site and data monitoring is conducted on all applicable studies at the Utah DCC. On-site monitoring is conducted according to project needs.

Remote Data Quality Monitoring: Continuous data quality monitoring is integral to assuring the highest quality data at the time of interim reports and accelerating database lock. REDCap handles field specific validation (such as range checks) and intra-form errors, potentially reducing accidental keystroke data entry errors. We do not *block* submission of data forms with range checks because this can cause the user to lose their work up to the point of the data discrepancy, and it is a natural tendency to create a “temporary value” with good faith intentions to later find the correct value and replace the temporary value. We prefer to prompt the user about range problems, but allow errant data to be entered, and we use the Query Manager ([see Facilities](#)) to assure later corrections. The Query Manager system also handles more complex data validation, such as between forms that are entered on different dates.

The Query Manager system allows the clinical data manager to monitor submitted data for discrepancies, and to write SQL-based triggers to notify users of data discrepancies. During the trial, new database triggers are written for unanticipated types of errors. Patterns of data entry errors or missingness are sought to provide feedback to sites, improving subsequent data quality. Such patterns may also indicate a need for retraining of site personnel about the database or data element definitions. When data errors are corrected by the site, discrepancies are automatically resolved; other types of discrepancies require communication in the system with the clinical data manager. Audit trails are maintained in the query system for all communications between the site and the clinical data manager.

As indicated previously, it is important to point out that the Query Manager system does *not* alter any data in the EDC nor in the SQL Server warehouse. All data entry into the EDC must be from an authorized user at the clinical sites, and the EDC maintains an audit trail of all database access as well as changes to data, in accordance with 21 CFR part 11 requirements. In rare instances, staff may make “self-evident” corrections such as an obvious year entry error between December 31 and January 1.

Study investigators, research coordinators, and NIH staff can view real time reports by specific clinical sites or individual query rules, by date of occurrence and resolution, or by aging of queries ([Figure 3 next page](#)). This software provides a powerful management tool for monitoring data quality in networks or trials that we coordinate.

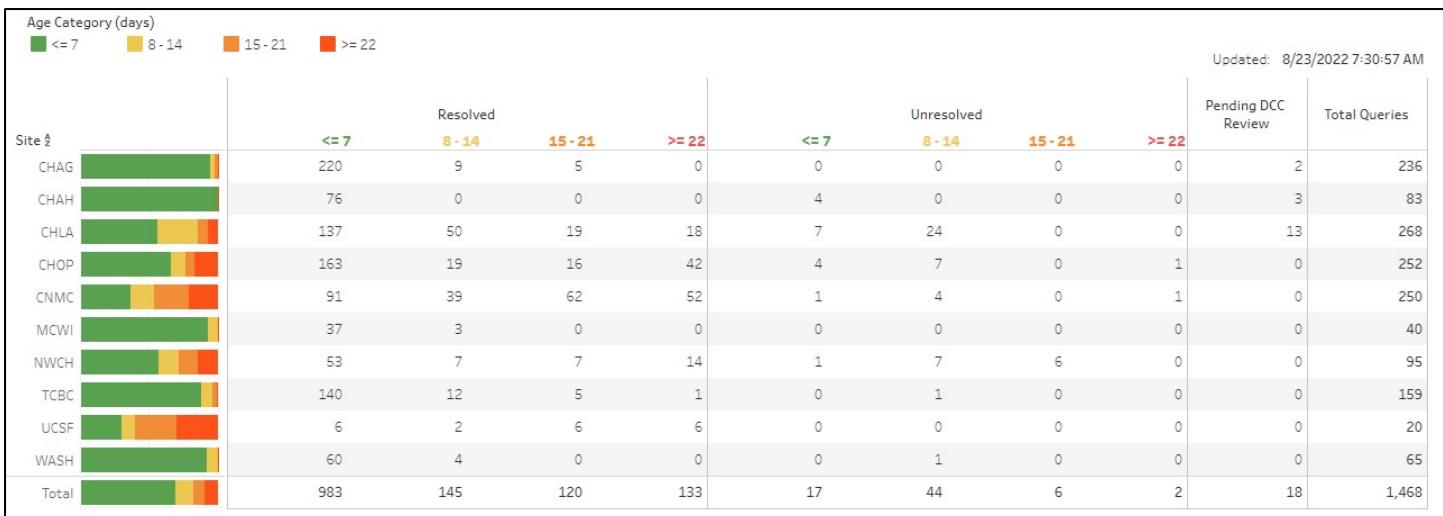


Figure 3 Query system aging dashboard to track queries to resolution

Remote-Site Monitoring: Remote-site monitoring is conducted on all applicable studies at the Utah DCC and helps to evaluate site compliance with GCP standards and regulatory requirements. Monitoring requirements are documented in the Trial Master File (TMF) and may include review of minimum required essential documents such as protocol requirements, IRB of record, sponsor requirements, and applicable regulations.

On-Site monitoring: Source data monitoring is performed according the overall study risk level, and may be adjusted throughout the study. Source data monitoring may be performed following enrollment of the first participant(s). A risk-based monitoring plan (RBMP) is used to identify the participants to be monitored (either pre-specified or randomly selected), to identify the data elements to be monitored, considering key eligibility criteria, primary outcomes, and adverse events, and to consider critical study processes, including informed consent. In addition, timing and frequency of monitoring activities are defined in the RBMP.

Technology transfer, data management, and protocol training capabilities

Technology Transfer Capabilities. The Information Technology (IT) group at the OPTICOM DCC is comprised of network infrastructure architects, system administrators, software design engineers, technical support analysts, business intelligence (BI) developers, data architects, and IT PM. The DCC offers end-to-end technical solutions to meet business needs, including the design and development of secure systems to receive, process, and store clinical research data.

Enterprise Infrastructure Architects design and implement the conceptual and logical information systems that support the enterprise infrastructure. The architect utilizes cross-functional knowledge in change management and business process management to ensure the underlying technical architecture and information systems meet the needs of the business. Systems Administrators maintain the entire technology stack, which includes the upkeep, configuration, and reliable operation of all servers, databases, systems, and permissions to those resources. Software Design Engineers work with product owners, PMs, program directors, and faculty to design and develop custom technical solutions, such as highly available web services, data transformation processes, websites, registry systems, and other innovative services. Technical Support Analysts provide in-person and remote technical support for users of DCC systems, including granting and troubleshooting permissions to DCC resources.

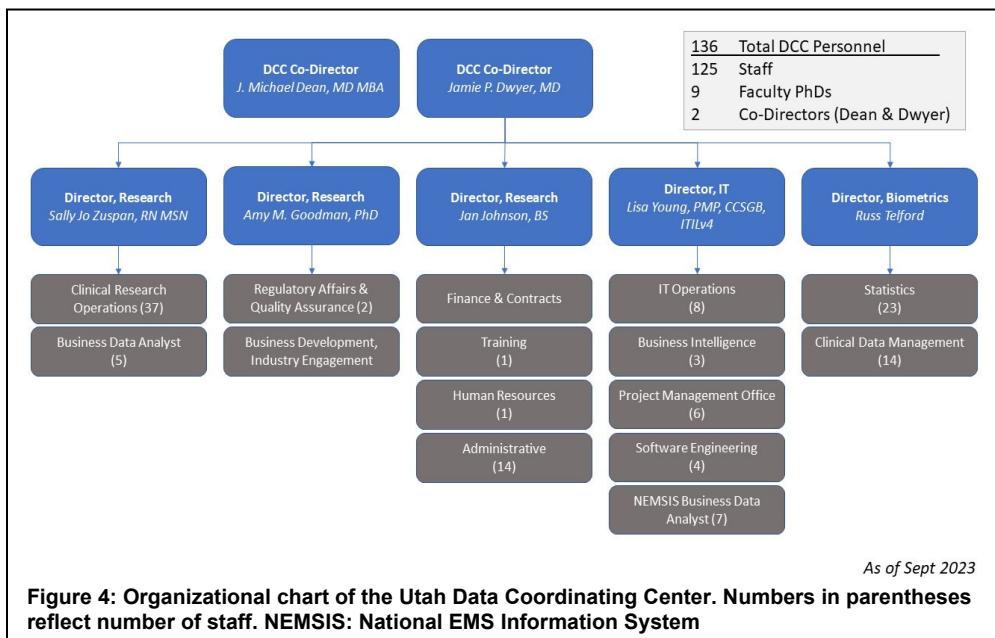
REDCap. REDCap is a secure web-based EDC system with robust features and advantages for participant-facing instruments such as eConsent or collection of patient reported outcomes (PROs). REDCap also has integration with a patient-facing application called MyCap. MyCap is a smart phone-based application that can be used by participants to provide information that is directly transmitted to the REDCap database. This app is available for Android and iOS platforms.

Protocol training capabilities. The DCC's preferred method for protocol and study training is to conduct a 1-2 day training session with all participating sites. These trainings may be in-person or remote. The site principal investigator and lead research coordinator must attend the training session, and sites are encouraged to bring additional staff.

For online training, the DCC offers the use of Moodle, an open-source free software product, to support online learning by investigational site personnel. Audio and video presentations can be embedded in the curriculum. Within the module, the user can start and stop the presentation at will, and at the end of the presentation, a quiz is provided. The software tracks individual users, and certificates are issued when a user has completed all the lessons and passed all the quizzes. We believe that online training is critical to complement training that occurs at investigator meetings and is particularly valuable in the context of research coordinators at multiple sites because of routine staff turnover.

Evidence of DCC administrative and management capabilities

The DCC is a full-service academic research organization (ARO) that provides comprehensive research support from concept development through protocol implementation and manuscript production. The DCC has a 21-year history supporting investigators from across the country to develop and implement a wide range of research projects and providing research support and expertise to multiple national clinical research networks. Our mission is to *accelerate research to the bedside for the benefit of patients across the lifespan*. We fulfill this mission by providing clinical and biostatistical leadership at the faculty level, statistical analysis, data management, project management, regulatory expertise, and comprehensive Information Technology (IT) systems to support multi-center clinical research. Our leadership brings substantial clinical expertise in pediatric and adult medicine, and our location inside an academic medical center provides access to clinical and research experts in many other areas. Drs. Dwyer and Dean provide stable leadership and broad experience in clinical research and grant writing. Dr. Goodman, Ms. Zuspan, and Ms. Johnson bring substantial clinical, operational, and clinical trial experience. Our leadership group is rounded out by experienced senior managers and directors (**Figure 4**).



Intent to participate in a cooperative manner with the NIH HEAL initiative and HEAL-KIDS Pain partners

We fully understand, accept and support the participatory and cooperative nature of the collaborative research process required in multicenter research. We accept the Cooperative Agreement Terms and Conditions of Award written in RFA-HD-24-011 "Cooperative Agreement Terms and Conditions of Award" and agree to participate in a cooperative, interactive and collaborative manner with members of the clinical trial project team, the HEAL KIDS Pain program team, the NIH HEAL Initiative, and the designated NIH staff (e.g., Program Officer(s) and Project Scientist(s)).

We currently serve as the Data Coordinating Resource Center (DCRC) for the HEAL Pain Management Effectiveness Research Network (ERN). As such, we have experience in working cooperatively with the NIH HEAL initiative, HEAL study teams and partners. We are uniquely trained through our past collaborative projects in the HEAL Pain ERN to work collaboratively with the NIH HEAL initiative and HEAL Kids Pain partners to 1) develop, implement, and monitor this HEAL KIDS trial; 2) help respond to issues/protocol changes that emerge during trial implementation and initiate timely necessary changes to assure trial success; 3) provide collection and analysis of data; and 4) assist with timely publication of study results.

POPULATION AVAILABLE FOR CLINICAL TRIAL

A **unique pediatric population** is available for enrollment in the OPTICOM trial, which will enroll children 0-18 years old with acute respiratory failure. Inclusion criteria have been deliberately designed to maximize patient eligibility, facilitating generalizability of findings to all children with ARF on MV, while still targeting the patient population who can most benefit from improved pain control.

CPCCRN sites account for 19% of children with acute respiratory failure in the entire US each year, and our selection of 14 study sites from within CPCCRN was designed to identify an ethnically and geographically diverse sample of eligible patients, in order to maximize compositional diversity of enrolled subjects. This will provide outstanding generalizability of our results to the larger pediatric critical care community. There is no other CPCCRN study focused on enrolling subjects with acute respiratory failure, so we do not anticipate limitations on patient availability.

Only a small portion of the 1000+ funded HEAL projects involve children – and **none** in the pediatric critical care space, where children are exposed to the highest doses of opioids. Of the ~24,000 children with acute respiratory failure admitted to PICUs in the United States each year, more than 50% are under two years of age. These very young children are exposed to high-dose, near-continuous opioids for extended periods of time. There is significant concern in the scientific community regarding the effects of opioids on the developing brain, yet this population has never been included in an adequately powered, multi-center RCT designed to improve pain control and decrease opioid exposure. This study will be the largest RCT exploring opioid-sparing agents in mechanically ventilated PICU infants and children.

Examples of patient populations available through the CPCCRN Network for the proposed OPTICOM trial are listed in the table below:

Race	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	1	1	2
Asian	1	1	2	3	7
Native Hawaiian or Other Pacific Islander	0	0	0	1	1
Black or African American	3	4	12	15	34
White	5	5	17	23	50
More than One Race	1	1	2	2	6
Total	10	11	34	45	100

HEAL PUBLIC ACCESS AND DATA SHARING POLICY

The **OPTICOM** research team agrees to abide by the HEAL Public Access and Data Sharing Policy. See the Data Management Sharing Plan (DMSP) for further details.

Publications resulting from NIH HEAL Initiative funded studies will be immediately publicly available upon publication. Prior to publication, HEAL expects investigators to alert program officers of upcoming manuscripts to ensure coordination of communication and outreach efforts. The OPTICOM team will acknowledge HEAL Initiative support by referencing in the acknowledgment sections of any relevant publication.

We will facilitate sharing of data from the HEAL Kids trial by incorporating HEAL Kids Common Data Elements (CDEs) into protocols and preparation of final data sets suitable for deposit in NIH designated repositories for incorporation into the HEAL Kids Data Ecosystem.

Incorporation of HEAL Common Data Elements

Common Data Elements (CDEs) provide structured human and machine-readable definitions of study data elements. We will collaborate with the **HEAL Kids RDC** and with other **HEAL Kids network** data coordinating centers to harmonize data elements and instruments/data collection forms, keeping in mind the potential high value in creating combined datasets that can be used for meta-analyses or other future studies of under-studied pain conditions. During protocol development, we work with study teams (and across studies) to identify common (shared) instruments, and to incorporate core and supplemental NIH HEAL Kids CDEs into protocols. Our team, including data managers and statisticians, will partner with the HEAL Kids RDC informatics experts to facilitate linking of study databases to the NIH HEAL Kids CDEs, and to verify that summary scores and analytics for patient reported outcomes and surveys correspond with validated metrics. The DCC has had a long-standing leadership in the Trial Innovation Network data harmonization working group and serves as the DCRC for the NIH HEAL program, which incorporates CDEs across studies. This knowledge will facilitate our trial's data harmonization efforts within the HEAL Kids network.

We will continue to work collaboratively with the NIH HEAL Kids program staff and RDC to create and maintain HEAL Kids CDEs. The DCC was instrumental in the documentation and formalization of HEAL CDEs across the HEAL program. Team members also have experience supporting the documentation of Spanish-language case report forms for core instruments and selected supplementary instruments.

Preparation of public-use datasets

After data lock, the OPTICOM DCC will prepare the trial database for public release, in accordance with the HEAL Public Access and Data Sharing policy. The DCC faculty and staff have extensive experience with preparation of such datasets. Data used for analyses are de-identified, a document with annotated case report forms or EDC screenshots is prepared, and a data dictionary is created. Data elements that are highly suspect or potentially sensitive are omitted from release, and this is explained in the documentation. Data can be provided as CSV files, or in SAS or other statistical formats. Instructions are provided to enable other investigators to import the data into their own analysis software systems. Cross tabulation summary reports are included, so that the user can verify that they can reproduce these in their own software systems. We have deposited NIH funded study data into the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) system, and into the NICHD Data and Specimen Hub (DASH) and are familiar with the curation requirements.

Incorporation of data into the HEAL Data Ecosystem

The HEAL Kids Data Ecosystem supports sharing of HEAL Kids-generated data and results, enabling HEAL Kids data to be searched, analyzed, and used to make new discoveries based on FAIR (findable, accessible, interoperable, and reusable) principles. The DCC has an existing close collaboration with the HEAL Data Ecosystem staff to support studies in the selection of data repositories and preparing HEAL generated data for sharing. This experience and relationship will be valuable when incorporating HEAL Kids data into the HEAL Data Ecosystem.

BIOSPECIMEN PLAN

NOT APPLICABLE. The OPTICOM program will not collect or exchange any biospecimens.

PLAN FOR ENHANCING DIVERSE PERSPECTIVES (PEDP) - OPTICOM

Significance: Acute Respiratory Failure (ARF) affects >24,000 children each year, with a disproportionate impact on Hispanic and Black children. These children require invasive mechanical ventilation (MV), which causes acute pain. A large body of literature shows that disparity health populations (based on race, ethnicity, socioeconomic status, education level, and limited English proficiency) are more likely to be undertreated for pain. These same families are also under-represented in clinical research studies. The OPTICOM study addresses these issues with an evidence-based approach that includes: (i) deliberate inclusion of diverse perspectives, expertise, and personnel in study design and execution, and (ii) explicit education of study staff in implicit bias and empathy training to improve compositional diversity of enrolled children. The OPTICOM team has developed a sophisticated PEDP to enhance significance of study results for ALL critically ill children.

Diversity in Our Research Team: Our team incorporates a wide perspective into study design and execution by including pediatricians, intensivists, nurses, pain specialists, ethicists, PICU patients and their parents. We proudly represent a diverse mix of genders, ethnicities, backgrounds, career stages, and a vibrant array of personalities. We have recruited junior faculty members, historically underrepresented in clinical research, as co-investigators, with strong mentorship provided by key personnel.

Innovation: Enrolled participants need to accurately reflect the population affected by the disease under study. Modifiable barriers to enrollment have been identified and include: implicit bias, cultural insensitivity, and selective approach by study staff. Evidence shows that explicit education can mitigate these barriers. Our multi-step PEDP will provide education to study staff on the history of racism in pain management, implicit bias, and best-practices in approaching and enrolling a diverse population.

Approach: To increase enrollment of patients generally under-represented in pediatric critical care research, we have deployed a visibly diverse study team to reduce medical mistrust and communication barriers. Outreach efforts will include parents of former PICU patients. We have brought in experts who will evaluate disparities in research enrollment and participation and provide guidance and training as needed. Study materials will be culturally and linguistically sensitive and accessible. Recruitment efforts, including the consenting process, will be done with respect, sensitivity, and attention to the unique circumstances of each parent. Throughout the study period, we will review approach rates of eligible patients, reasons for parental refusal, and demographic composition of enrolled children, and provide corrective action if needed.

Environment: OPTICOM will be implemented by the Collaborative Pediatric Critical Care Research Network (CPCCRN) and centralized Data Coordinating Center (DCC). CPCCRN includes a Family Network Collaborative to provide a community-based perspective. OPTICOM has selected 14 clinical sites from within CPCRRN to maximize geographic, racial, and socioeconomic diversity of the study population, and have ensured that full-time translator services are available at all sites.

Timeline: A summary of strategies and timeline for core PEDP milestones are as follows:

	Year 1									Year 2			Year 3			Year 4			Year 5					
	M1 0	M2 1	M3 1	M4 2	M5 3	M6 4	M7 5	M8 6	M9 7	M10 8	M11 9	M12 0	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Study Initiation																								
Steering Committee established	X																							
PEDP Plan finalized		X																						
PEDP Curriculum for study sites:																								
History of racism in pain management		X																						
Implicit Bias I			X																					
Implicit Bias II			X																					
Missing Voices: Underrepresented Populations in Pediatric Research				X																				
Enhancing Compositional Diversity I					X																			
Enhancing Compositional Diversity II						X																		
Enrollment Period																								
Site Activation							X																	
PEDP/Steering Committee Meetings	X		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Site-Specific PEDP Reviews (as needed)								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Executive Team Meetings (HEAL-KIDS)	X		X					X			X			X			X			X		X	X	X
Publication Plan Finalized									X															

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator				
Prefix: Dr.	First Name*: Chani	Middle Name	Last Name*: Traube	Suffix:
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County:	New York			
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
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E-Mail*:	chr9008@med.cornell.edu			
Credential, e.g., agency login:	CTRAUBE			
Project Role*:	PD/PI			
	Other Project Role Category:			
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name:	Traube_Biosketch_final.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person				
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Division:	None			
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Street2:				
City*:	Washington			
County:				
State*:	DC: District of Columbia			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	20010-2970			
Phone Number*:	888-884-2327		Fax Number:	
E-Mail*:	mbell@childrensnational.org			
Credential, e.g., agency login:	MJBELL			
Project Role*:	PD/PI		Other Project Role Category:	
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name:	Bell_Biosketch_final.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person				
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City*:	Salt Lake City			
County:				
State*:	UT: Utah			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	84112-8906			
Phone Number*:	801-213-4172		Fax Number:	
E-Mail*:	richard.holubkov@hsc.utah.edu			
Credential, e.g., agency login:	RHOLUBKOV			
Project Role*:	PD/PI		Other Project Role Category:	
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name:	Holubkov, Richard.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person				
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Department:	Pediatrics/School of Medicine			
Division:	None			
Street1*:	733 N. Broadway, Suite 117			
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State*:	MD: Maryland			
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Phone Number*:	410.955.7609		Fax Number:	
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Project Role*: Other (Specify)	Other Project Role Category: SubAward PI			
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name:	Kudchadkar_Biosketch_final.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person				
Prefix:	First Name*: Erin	Middle Name D	Last Name*: Paquette	Suffix:
Position/Title*:				
Organization Name*:	Ann & Robert H Lurie Childrens Hospital of Chicago			
Department:	Ann & Robert H Lurie Childrens Hospital of Chicago			
Division:	None			
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Phone Number*:	312-227-4800		Fax Number:	
E-Mail*:	EPaquette@luriechildrens.org			
Credential, e.g., agency login:	etalati			
Project Role*: Other (Specify)	Other Project Role Category: SubAward PI			
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name:	Paquette_Biosketch.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person				
Prefix: Dr.	First Name*: Joy	Middle Name	Last Name*: Howell	Suffix:
Position/Title*:	Professor of Clinical Pediatrics			
Organization Name*:	Joan and Sanford I Weill Medical College			
Department:	Pediatrics			
Division:	None			
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State*:	NY: New York			
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Zip / Postal Code*:	10065-0000			
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E-Mail*:	jdh2002@med.cornell.edu			
Credential, e.g., agency login:	JOYHOWELL			
Project Role*:	Co-Investigator		Other Project Role Category:	
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name:	Howell_Biosketch.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person				
Prefix:	First Name*: Vanessa	Middle Name	Last Name*: Madrigal	Suffix:
Position/Title*:				
Organization Name*:	Children's Research Institute			
Department:	Children's Research Institute			
Division:	None			
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County:				
State*:	DC: District of Columbia			
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Project Role*:	Co-Investigator		Other Project Role Category:	
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name:	Madrigal_Biosketch.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person				
Prefix:	First Name*: Ron	Middle Name W	Last Name*: Reeder	Suffix:
Position/Title*:	Associate Professor			
Organization Name*:	University of Utah			
Department:	Department of Pediatrics			
Division:	None			
Street1*:	201 S. President's Circle, Rm 210			
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City*:	Salt Lake City			
County:				
State*:	UT: Utah			
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Country*:	USA: UNITED STATES			
Zip / Postal Code*:	84112-8906			
Phone Number*:	801-662-5400		Fax Number:	
E-Mail*:	Ron.Reeder@hsc.utah.edu			
Credential, e.g., agency login:	rreeder			
Project Role*:	Co-Investigator		Other Project Role Category:	
Degree Type:	Degree Year:			
Attach Biographical Sketch*:	File Name:	Reeder_Biosketch_final.pdf		
Attach Current & Pending Support:	File Name:			

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Chani Traube

ERA COMMONS USER NAME (credential, e.g., agency login): ctraube

POSITION TITLE: Professor of Pediatrics, Weill Cornell Medicine

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Yeshiva University, New York, NY	B.A.	06/1995	Judaic Studies
Albert Einstein College of Medicine, Bronx, NY	M.D.	06/2000	Medicine
NY Presbyterian Hospital—Weill Cornell Medical College, New York, NY	OTH	06/2003	Internship and Residency, Pediatrics
NY Presbyterian Hospital—Weill Cornell Medical College, New York, NY	OTH	06/2006	Fellowship, Pediatric Critical Care Medicine

A. Personal Statement

I am a Professor of Pediatrics in the Division of Pediatric Critical Care, Director of Clinical Research Mentoring for the Department of Pediatrics at Weill Cornell Medicine, and a clinical researcher with expertise in pediatrics, pediatric critical illness, delirium, and PICU outcomes.

I currently serve as the Steering Committee Chair for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN), a multicenter program devoted to development and execution of large clinical trials to investigate the safety and efficacy of treatment management strategies used for the care of critically ill and injured children.

I am a founding member of the Weill Cornell Delirium Work Group (DWG), which developed and validated the Cornell Assessment of Pediatric Delirium, a bedside delirium screening tool now used as standard-of-care for hospitalized children in academic PICUs worldwide. I lead a multidisciplinary team of clinicians and researchers who spearhead research on long-term outcomes in child survivors and their families after pediatric critical care. I am currently MPI on a multi-site study investigating the relationship between the pharmacokinetics of sedatives and delirium. I am also the PI on a National Cancer Institute-funded multi-site study investigating the epidemiology of delirium and long-term cognitive outcomes in children undergoing stem cell transplantation. My recent research has been focused on parental mental health symptomatology after a child's PICU stay, with an award-winning presentation at the Society of Critical Care Medicine Annual Congress in April 2022. Thus, I have the extensive experience in leading multi-site studies, operationalizing studies in the complex PICU environment, and directing multi-disciplinary collaborative teams, which are essential to the success of this study.

Ongoing projects that I would like to highlight include:

R01 CA244500

Traube (PI)

09/01/2020-05/31/2025

Delirium in Children Undergoing Hematopoietic Stem Cell Transplants

R01 HD099284

Bell, Empey, Traube (MPI)

09/01/2019-07/31/2024

Pharmacokinetics of Sedatives – Understanding a Modifiable Risk Factor for Pediatric Delirium

Citations I would like to highlight include:

1. **Traube C**, Silver G, Kearney J, Patel A, Atkinson TM, Yoon MJ, Halpert S, Augenstein J, Sickles LE, Li C, Greenwald B. Cornell Assessment of Pediatric Delirium: a valid, rapid, observational tool for screening delirium in the PICU*. Crit Care Med. 2014 Mar;42(3):656-63. doi: 10.1097/CCM.0b013e3182a66b76. PMID: 24145848; PMCID: PMC5527829.
2. **Traube C**, Silver G, Reeder RW, Doyle H, Hegel E, Wolfe HA, Schneller C, Chung MG, Dervan LA, DiGennaro JL, Buttram SD, Kudchadkar SR, Madden K, Hartman ME, deAlmeida ML, Walson K, Ista E, Baarslag MA, Salonia R, Beca J, Long D, Kawai Y, Cheifetz IM, Gelvez J, Truemper EJ, Smith RL, Peters ME, O'Meara AM, Murphy S, Bokhary A, Greenwald BM, Bell MJ. Delirium in Critically Ill Children: An International Point Prevalence Study. Crit Care Med. 2017 Apr;45(4):584-590. doi: 10.1097/CCM.0000000000002250. PMID: 28079605; PMCID: PMC5350030.
3. **Traube C**, Gerber LM, Mauer EA, Small K, Broglie L, Chopra YR, Duncan CN, Ebens CL, Fitzgerald JC, Freedman JL, Hudspeth MP, Hurley C, Mahadeo KM, McArthur J, Shapiro MC, Sharron MP, Wall DA, Zinter MS, Greenwald BM, Silver G, Boulad F. Delirium in Children Undergoing Hematopoietic Cell Transplantation: A Multi-Institutional Point Prevalence Study. Front Oncol. 2021 Apr 22;11:627726. doi: 10.3389/fonc.2021.627726. PMID: 33968727; PMCID: PMC8100670.
4. **Traube C**, Tucci M, Nellis ME, Avery KL, McQuillen PS, Fitzgerald JC, Muszynski JA, Cholette JM, Schwarz AJ, Stalets EL, Quaid MA, Hanson SJ, Lacroix J, Reeder RW, Spinella PC; Transfusion-Associated Delirium ABC-PICU Study Group. Transfusion-Associated Delirium in Children: No Difference Between Short Storage Versus Standard Issue RBCs. Crit Care Med. 2022 Feb 1;50(2):173-182. doi: 10.1097/CCM.0000000000005393. PMID: 35100190; PMCID: PMC8820396.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021 – Present	Professor of Pediatrics, Weill Cornell Medical College, New York, NY
2023 – Present	Chair, Steering Committee Chair for the NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN)
2021 – 2023	Chair, Data Safety Monitoring Board for the CPCCRN study “PRECISE”
2012 – 2021	Associate Professor of Pediatrics, Weill Cornell Medical College, New York, NY
2010	Member, NIH T32 Review for Pediatric Neurointensive Care and Resuscitation Research Program
2009	Member, NIH study subsection for Collaborative Pediatric Care Research Network (CPCCRN), Review committee for RFA's at NICHD/NIH
2006 – Present	Assistant Professor of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY
2006 – Present	Board Certified, Pediatric Critical Care, American Board of Pediatrics
2003 – Present	Board Certified, Pediatrics, American Board of Pediatrics
2003 – Present	Member, NY Society of Pediatric Critical Care Medicine
2003 – Present	Member, Society of Critical Care Medicine
2000 – Present	Member, American Academy of Pediatrics

Honors

2019 – 2020	Chair, ICU Liberation Committee, Society of Critical Care Medicine
2018 – 2019	Vice-Chair, ICU Liberation Committee, Society of Critical Care Medicine
2018	ICU Hero Award, Society of Critical Care Medicine
2016	AI McGuire Memorial Lecture, Children's Hospital of Wisconsin
2016	Fellowship in the Society of Critical Care Medicine

C. Contributions to Science

1. **Development, validation, and dissemination of a screening tool for diagnosing delirium in children:** Delirium is defined as an acute change in awareness and cognition that occurs in the setting of an underlying illness. Without routine screening, the majority of delirium cases remain undetected until they are severe. Until recently, a barrier to delirium detection in children was the unavailability of a feasible bedside screen. Our tool, the Cornell Assessment for Pediatric Delirium (CAPD), has been demonstrated to have excellent validity and reliability in children of all ages (concordance 97%, sensitivity 92%, specificity 87%). As a result of our work, delirium screening has now become the standard of care in critically ill children, and delirium prevention and management programs have been implemented in many PICUs. This has not only improved clinical care but has also enabled large-scale pediatric delirium research. I served as PI for all of these studies:
 - a. Silver G, **Traube C**, Kearney J, Kelly D, Yoon MJ, Nash Moyal W, Gangopadhyay M, Shao H, Ward MJ. Detecting pediatric delirium: development of a rapid observational assessment tool. *Intensive Care Med.* 2012 Jun;38(6):1025-31. doi: 10.1007/s00134-012-2518-z. Epub 2012 Mar 10. PMID: 22407142.
 - b. Silver G, Kearney J, **Traube C**, Atkinson TM, Wyka KE, Walkup J. Pediatric delirium: evaluating the gold standard. *Palliat Support Care.* 2015 Jun;13(3):513-6. doi: 10.1017/S1478951514000212. Epub 2014 Apr 24. PMID: 24762563; PMCID: PMC4968931.
 - c. Silver G, Kearney J, **Traube C**, Hertzig M. Delirium screening anchored in child development: The Cornell Assessment for Pediatric Delirium. *Palliat Support Care.* 2015 Aug;13(4):1005-11. doi: 10.1017/S1478951514000947. Epub 2014 Aug 15. PMID: 25127028; PMCID: PMC5031084.
 - d. Kaur S, Silver G, Samuels S, Rosen AH, Weiss M, Mauer EA, Gerber LM, Greenwald BM, **Traube C**. Delirium and Developmental Disability: Improving Specificity of a Pediatric Delirium Screen. *Pediatr Crit Care Med.* 2020 May;21(5):409-414. doi: 10.1097/PCC.0000000000002248. PMID: 32106184.
2. **Outcomes in children and families after critical illness:** Our single- and multi-center studies have shown that the impact of critical illness does not end when the child is discharged from the PICU. I have designed studies to describe and prevent Post Intensive Care Syndrome (PICS), defined as impairments in the physical and mental health and functioning of both patients and family caregivers following the patient's ICU stay. Our research revealed that parents of children in the Pediatric ICU (PICU) exhibit alarmingly high rates of psychological distress. As studies show that parents' mental health influences family health, I have recognized the importance of addressing parental mental health issues in order to improve long term outcomes for my patients and their families. As a member of the Pediatric Outcomes STudies after PICU (POST-PICU) Investigators Network, with a specific focus on family outcomes, I have been instrumental in defining a core outcome set for pediatric critical care.
 - a. **Traube C**, Silver G, Gerber LM, Kaur S, Mauer EA, Kerson A, Joyce C, Greenwald BM. Delirium and Mortality in Critically Ill Children: Epidemiology and Outcomes of Pediatric Delirium. *Crit Care Med.* 2017 May;45(5):891-898. doi: 10.1097/CCM.0000000000002324. PMID: 28288026; PMCID: PMC5392157.
 - b. Silver G, Doyle H, Hegel E, Kaur S, Mauer EA, Gerber LM, **Traube C**. Association Between Pediatric Delirium and Quality of Life After Discharge. *Crit Care Med.* 2020 Dec;48(12):1829-1834. doi: 10.1097/CCM.0000000000004661. PMID: 33031144; PMCID: PMC8195312.
 - c. Maddux AB, Pinto N, Fink EL, Hartman ME, Nett S, Biagas K, Killien EY, Dervan LA, Christie LM, Luckett PM, Loftis L, Lackey M, Ringwood M, Smith M, Olson L, Sorenson S, Meert KL, Notterman DA, Pollack MM, Mourani PM, Watson RS; Pediatric Outcomes STudies after PICU (POST-PICU) and PICU-COS Investigators of the Pediatric Acute Lung Injury and Sepsis Investigators and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Networks. Postdischarge Outcome Domains in Pediatric Critical Care and the Instruments Used to Evaluate Them: A Scoping Review. *Crit Care Med.* 2020 Dec;48(12):e1313-e1321. doi: 10.1097/CCM.0000000000004595. PMID: 33009099; PMCID: PMC7708523.

- d. O'Meara A, Akande M, Yagiela L, Hummel K, Whyte-Nesfield M, Michelson KN, Radman M, **Traube C**, Manning JC, Hartman ME. Family Outcomes After the Pediatric Intensive Care Unit: A Scoping Review. *J Intensive Care Med.* 2022 Sep;37(9):1179-1198. doi: 10.1177/08850666211056603. Epub 2021 Dec 17. PMID: 34919003.
3. **Epidemiology and associated risk factors for pediatric delirium:** Delirium affects approximately one out of four critically ill children, with an incidence of >45% in children after cardiac bypass surgery, and >50% rates in children on invasive mechanical ventilation. Our research has shown increased delirium risk in younger children (< 5y), those with developmental disabilities, increased severity of illness, and need for mechanical ventilation. It is most important to identify strategies to prevent delirium by focusing on specific modifiable risk factors: we have identified that precipitating factors include immobility, sedation, and RBC transfusions. This provides actionable information for pediatric intensivists, and vital information for future research studies. I served as PI, and either first- or last-author on all of these studies:
 - a. Patel AK, Biagas KV, Clarke EC, Gerber LM, Mauer E, Silver G, Chai P, Corda R, **Traube C**. Delirium in Children After Cardiac Bypass Surgery. *Pediatr Crit Care Med.* 2017 Feb;18(2):165-171. doi: 10.1097/PCC.0000000000001032. PMID: 27977539; PMCID: PMC5658045.
 - b. Meyburg J, Dill ML, von Haken R, Picardi S, Westhoff JH, Silver G, **Traube C**. Risk Factors for the Development of Postoperative Delirium in Pediatric Intensive Care Patients. *Pediatr Crit Care Med.* 2018 Oct;19(10):e514-e521. doi: 10.1097/PCC.0000000000001681. PMID: 30059477.
 - c. Dechnik A, Mauer EA, Gerber LM, **Traube C**. C-Reactive Protein and Procalcitonin Levels May Not Predict Delirium in Critically Ill Children. *Pediatr Crit Care Med.* 2020 Nov;21(11):e967-e971. doi: 10.1097/PCC.0000000000002412. PMID: 32433442; PMCID: PMC8177727.
 - d. **Traube C**, Tucci M, Nellis ME, Avery KL, McQuillen PS, Fitzgerald JC, Muszynski JA, Cholette JM, Schwarz AJ, Stalets EL, Quaid MA, Hanson SJ, Lacroix J, Reeder RW, Spinella PC; Transfusion-Associated Delirium ABC-PICU Study Group. Transfusion-Associated Delirium in Children: No Difference Between Short Storage Versus Standard Issue RBCs. *Crit Care Med.* 2022 Feb 1;50(2):173-182. doi: 10.1097/CCM.0000000000005393. PMID: 35100190; PMCID: PMC8820396.
4. **Measurement and optimization of sedation in pediatric critical illness.** Consistent with studies from adults, we have found a consistent relationship between benzodiazepine administration and poor outcomes. The association between sedative depth, choice of agent, and pediatric delirium is strong and represents the main modifiable risk factor. Thus, I believe that an in-depth understanding of best-practices with respect to pediatric sedation is vital to advance the field and improve long-term pediatric outcomes. I served as PI or Co-Investigator on these studies:
 - a. Kerson AG, DeMaria R, Mauer E, Joyce C, Gerber LM, Greenwald BM, Silver G, **Traube C**. Validity of the Richmond Agitation-Sedation Scale (RASS) in critically ill children. *J Intensive Care.* 2016 Oct 26;4:65. doi: 10.1186/s40560-016-0189-5. PMID: 27800163; PMCID: PMC5080705.
 - b. Zimmerman KO, Smith PB, Benjamin DK, Laughon M, Clark R, **Traube C**, Stürmer T, Hornik CP. Sedation, Analgesia, and Paralysis during Mechanical Ventilation of Premature Infants. *J Pediatr.* 2017 Jan;180:99-104.e1. doi: 10.1016/j.jpeds.2016.07.001. Epub 2016 Aug 10. PMID: 27522446; PMCID: PMC5183489.
 - c. Mody K, Kaur S, Mauer EA, Gerber LM, Greenwald BM, Silver G, **Traube C**. Benzodiazepines and Development of Delirium in Critically Ill Children: Estimating the Causal Effect. *Crit Care Med.* 2018 Sep;46(9):1486-1491. doi: 10.1097/CCM.0000000000003194. PMID: 29727363; PMCID: PMC6095819.
 - d. Shildt N, **Traube C**, Dealmeida M, Dave I, Gillespie S, Moore W, Long LD, Kamat PP. "Difficult to Sedate": Successful Implementation of a Benzodiazepine-Sparing Analgosedation-Protocol in Mechanically Ventilated Children. *Children (Basel).* 2021 Apr 28;8(5):348. doi: 10.3390/children8050348. PMID: 33924822; PMCID: PMC8146538.
5. **Treatment options for pediatric delirium:** Importantly, delirium is treatable and preventable. Studies show that implementation of a multi-component prevention protocol in adults -- with establishment of routine delirium screening, minimization of benzodiazepine-based sedation, and early mobilization -- can significantly decrease the incidence of delirium and improve outcomes. Our goal is to develop national

pediatric delirium prevention guidelines that will decrease delirium rates and improve long-term outcomes in children. I served as the primary investigator, and first- or last-author in all of these studies:

- a. **Traube C**, Witcher R, Mendez-Rico E, Silver G. Quetiapine as treatment for delirium in critically ill children: A case series. *J Pediatr Intensive Care*. 2013 Sep;2(3):121-126. doi: 10.3233/PIC-13060. PMID: 31214433; PMCID: PMC6530724.
- b. Joyce C, Witcher R, Herrup E, Kaur S, Mendez-Rico E, Silver G, Greenwald BM, **Traube C**. Evaluation of the Safety of Quetiapine in Treating Delirium in Critically Ill Children: A Retrospective Review. *J Child Adolesc Psychopharmacol*. 2015 Nov;25(9):666-70. doi: 10.1089/cap.2015.0093. Epub 2015 Oct 15. PMID: 26469214; PMCID: PMC4808274.
- c. **Traube C**. All Delirium May Not Be Created Equal: Consideration of Differential Effects of Delirium Based Upon Underlying Etiology. *Pediatr Crit Care Med*. 2018 Oct;19(10):1009-1010. doi: 10.1097/PCC.0000000000001704. PMID: 30281574.
- d. Silver G, **Traube C**. A systematic approach to family engagement: Feasibility pilot of a pediatric delirium management and prevention toolkit. *Palliat Support Care*. 2019 Feb;17(1):42-45. doi: 10.1017/S1478951518000895. Epub 2019 Jan 31. PMID: 30700336.

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/chani.traube.1/bibliography/49350769/public/?sort=date&direction=ascending>

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Michael J. Bell, MD

ERA COMMONS USERNAME (credential, e.g., agency login): MJBELL
ORCID Number – 0000-0001-8428-2567

POSITION TITLE: Professor with Tenure of Pediatrics; Chief, Pediatric Critical Care Medicine; Endowed Chair of Pediatric Critical Care Medicine; Children's National Hospital and The George Washington University School of Medicine

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Cornell University	B.S.	06/1987	Biology
SUNY HSC at Brooklyn	M.D.	06/1991	Medicine
St. Christopher's Hospital for Children	Resident	06/1994	Pediatrics
University of Pittsburgh School of Medicine	Fellow	06/1997	Pediatric Critical Care Medicine

A. Personal Statement

I am a Professor with Tenure of Pediatrics as well as Division Chief for Pediatric Critical Care Medicine and an Endowed Chair for Pediatric Critical Care Medicine at Children's National Hospital and The George Washington University School of Medicine. For the vast majority of my academic career, I have had research interests that combined the understanding of caring for children with critical illnesses with a sharp focus on the care of children with neurological conditions. As a young faculty member at Children's National Medical Center in 1998, I earned a K12 grant working on the effect of inflammation on the brain development of rodents. This work was continued in 2003 into a K08 application that expanded the work to determine the effect of intrauterine inflammatory stimuli on oligodendrocyte development in rats and mice. During this time, I founded the clinical Neurocritical Care service at Children's National for the care of children with critical brain injuries. I was recruited to the University of Pittsburgh in 2007 to organize and lead their Pediatric Neurocritical Care and Pediatric Neurotrauma teams --- for both expertise in clinical care and to perform cutting-edge research within the University. At the University of Pittsburgh, I was the site Principal Investigator for the Cool Kids Trial of hypothermia for children with severe traumatic brain injury, and then was the Principal Investigator for the Multiple Medical Therapies for Severe Pediatric TBI (also called the Approaches and Decisions for Acute Pediatric TBI [ADAPT] Trial) that was funded by NINDS. In this study, over 50 clinical sites enrolled 1000 children to prove 6 hypotheses related to the care of children with severe traumatic brain injury – the leading cause of death of children between the age of 1-18 y.

My current academic efforts continue in the realm of understanding how to care for children with neurological and other critical illnesses. To that end, Dr. Traube and I have been conducting a multi-centered study of how medications might result in pediatric delirium in children with acute respiratory failure. The preliminary data from this observational study in pediatric delirium provides important justifications for OPTICOM and we believe OPTICOM represents the next necessary step to providing evidenced-based guidelines for children with acute respiratory failure. Also, directly relevant to this application, I have led multi-centered studies in children for over a decade and I am a recognized expert in the field of pediatric critical care medicine. I have been a member of CPCCRN – the network within which this study will be conducted – since 2004. In addition

to this work in acute respiratory failure, I am currently working with sites in Argentina and Paraguay to understand how compliance with evidenced-based guidelines for severe traumatic brain injury are related to outcomes in this region that largely did not contribute literature to these guidelines. I am collaborating with others to understand how brain biomarkers may relate to acquired brain injury of children while on extracorporeal membrane oxygenation (ECMO) for severe cardiac/respiratory failure. Lastly, I'm collaborating with others to perform a randomized trial of azithromycin to treat RSV-induced respiratory failure in infants.

Ongoing and recently completed projects that I would like to highlight include:

RL1 HD107781

Bell (PI)

04/01/2021-05/31/2026

Collaborative Pediatric Critical Care Research Network platform trials to treat multiple organ failure in critically ill children

R01 NS106560

Bell (PI)

01/01/2019-12/31/2023

Implementation science proposal to determine the role of adherence to TBI guidelines in outcomes in 16 centers in South America

R01 HD099284

Bell (PI)

09/01/2019-07/31/2024

Understanding the pharmacodynamics of sedatives as a modifiable risk factor for delirium in critically ill children

R01 NS106292

Bembea (PI); role – Co-I

09/01/2018-08/31/2023

Determining of blood-derived biomarkers can predict neurological injury in children on ECMO

R01 HD105678

Kong (PI); role – Co-I

08/01/2020-07/31/2024

A phase III of azithromycin to decrease illness severity in children with RSV-induced respiratory failure

Citations I would like to highlight:

1. Kochanek PM, Tasker RC, Carney N, Totten AM, Adelson PD, Selden NR, Davis-O'Reilly C, Hart EL, **Bell MJ**, Bratton SL, Grant GA, Kissoon N, Reuter-Rice KE, Vavilala MS, Wainwright MS. Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition: Update of the Brain Trauma Foundation Guidelines, Executive Summary. *Pediatr Crit Care Med* 20(3):280-289, 2019. PMID: 30830016.
2. **Bell MJ**, Rosario BL, Kochanek PM, Adelson PD, Morris KP, Au AK, Schober M, Butt W, Edwards RJ, Zimmerman J, Pineda J, Le TM, Dean N, Whalen MJ, Figaji A, Luther J, Beers SR, Gupta DK, Carpenter J, Buttram S, Wisniewski SR and the ADAPT Investigators. Comparative Effectiveness of Diversion of Cerebrospinal Fluid for Children with Severe Traumatic Brain Injury. *JAMA Netw Open* 5(7):e2220969, 2022. PMID: 35802371.
3. Kochanek PM, Adelson PD, Rosario BL, Hutchison J, Miller Ferguson N, Ferrazzano P, O'Brien N, Beca J, Sarnaik A, LaRovere K, Bennett TD, Deep A, Gupta D, Willyerd FA, Gao S, Wisniewski SR, **Bell MJ**; ADAPT Investigators. Comparison of Intracranial Hypertension Measurements Before and After Hypertonic Saline or Mannitol Treatment in Children with Severe Traumatic Brain Injury. *JAMA Netw Open*. 2022. Mar 1; 5(3); e220891. Doi: 10.1001/Jamanetworkopen.2022.0891. PMID: 35267036.
4. Feinberg C, Carr C, Zemek R, Yeates KO, Master C, Schneider K, **Bell MJ**, Wisniewski S, Mannix R. Association of Pharmacological Interventions with Symptom Burden Reduction in Patients with Mild Traumatic Brain Injury: A Systematic Review. *JAMA Neurol* 78(5): 596-608, 2021. PMID: 33464290.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

- 2017 – Professor, Pediatrics and Critical Care Medicine, The George Washington University School of Medicine and Children's National Medical Center, Washington, DC
2017 – Chief, Pediatric Critical Care Medicine, Children's National Medical Center, Washington, DC
2017 – DC Lawyers Care for Children Endowed Professor of Pediatric Critical Care Medicine, Children's National Hospital, Washington DC
2013 – Professor, Critical Care Medicine, Neurological Surgery and Pediatrics, University of Pittsburgh
2008 – Associate Director for Pediatric Neurointensive Care, Safar Center for Resuscitation Research
2008 – Director, Pediatric Neurotrauma Center, University of Pittsburgh
2008 – Associate Professor of Neurological Surgery, University of Pittsburgh
2007 – Associate Professor of Critical Care and Pediatrics, University of Pittsburgh, Pittsburgh, PA
2007 – Director, Neurocritical Care, Children's Hospital of Pittsburgh
2007 – Co-Director, Pediatric Neurotrauma Center, University of Pittsburgh
2005 – 2007 Director, Neurocritical Care, Children's National Medical Center
2000 – 2007 Member, Neuroscience Center, Children's Research Institute, Washington, DC
1997 – 2003 Assistant Professor of Pediatrics, Children's National Medical Center and George Washington University School of Medicine, Washington, DC
1997 – 2000 Special Volunteer, Stroke Branch, NINDS, NIH, Bethesda, MD

Honors

- 2007 - 2019 – Named to “Best Doctors in America”
1998, 1999, 2002, 2004 – “Golden Apple” Teaching Award, Children’s National Medical Center
1998 – In Training Fellow Award, Society of Critical Care Medicine
1997 – Finalist, National Neurotrauma Society Award
1997 – Educational Scholarship Award, Society of Critical Care Medicine
1996 – Finalist, National Neurotrauma Society Award

Licensed to practice medicine in the District of Columbia.

C. Contributions to Science

My contributions to science revolve around the study of brain injuries - with a focus on the young – and their translation of findings into clinical practice. Relevant to this application, I have outlined my reports regarding traumatic brain injury. Specifically, I have outlined my contributions related to (i) establishing standards for international studies, (ii) evidence from multi-center studies, (iii) evidence generated from preliminary data from ADAPT, (iv) single center studies that have informed clinical guidelines and (v) important associations between hypothermia (the therapy most often tested for children with severe TBI) and outcomes. **The following publications support representative examples of my contribution to each of these areas, selected from over 245 publications.**

1. *Establishing International Standards for Severe TBI*

Establishing evidenced-based guidelines and common data elements for reporting of data from clinical trials have been priorities toward improving clinical research for TBI. I have been a part of much of this work and continue to serve on the Brain Trauma Foundation committees to review evidence for guidelines for adults and children with severe TBI.

- a. Kochanek PM, Carney N, Adelson PD, Ashwal S, **Bell MJ**, Bratton S, Carson S, Chesnut RM, Ghajar J, Goldstein B, Grant GA, Kisssoon N, Peterson K, Selden N, Tasker RD, Vavilala MS, Wainwright MS, Warden CR. Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents, Second Edition. *Pediatr Crit Care Med* 13 (1 Suppl.): S1-82, 2012. PMID: 22217782.
- b. Carney N, Totten A, O'Reilly C, Ghajar J, **Bell MJ**, Bratton S, Chesnut R, Harris O, Hawryluk G, Kisssoon T, Rubiano A, Shutter L, Tasker R, Ullman J, Vavilala M, Wilberger J, Wright D.

- Guidelines for the Management of Severe Traumatic Brain Injury. Neurosurgery 2016 (in press). PMID 27654000.
- c. Adelson PD, Pineda J, **Bell MJ**, Abend NS, Berger RP, Giza C, Hotz G, Adelson PD. Common Data Elements for Pediatric Traumatic Brain Injury: Recommendations from the Working Group on Demographics and Clinical Assessment. *J Neurotrauma* 29(4): 639-653, 2012. PMID: 21939389.
 - d. **Bell MJ** and Wisniewski SR. Severe Traumatic Brain Injury in Children – A Vision for the Future. *Intensive Care Med* 42 (10): 1618-20, 2016. PMID: 27256038.
2. *Literature that forms the basis of evidenced-based practice in pediatric TBI from multi-centered studies*
As outlined above, I have worked in a number of consortia to determine best practices for children with TBI.
- a. Vavilala MS, Kernic MA, Wang J, Kannan N, Mink RB, Wainwright MS, Groner JI, **Bell MJ**, Giza CC, Zatzick DF, Ellenbogen RG, Boyle LN, Mitchell PH, Rivara FP for the PEGASUS study. Acute Care Clinical Indicators Associated with Discharge Outcomes in Children with Severe Traumatic Brain Injury. *Crit Care Med* 42(10): 2258-66, 2014. PMID: 25083982.
 - b. Cleve W, Kernic MA, Ellenbogen RG, Wang J, Zatnick DF, **Bell MJ**, Wainwright MS, Groner JI, Mink RB, Giza CC, Boyle L, Mitchell PH, Rivara FP, Vavilala MS and PEGASUS working group (Pediatric Guideline Adherence and Outcomes Project). National variability in intracranial pressure monitoring and decompressive craniotomy for children with moderate to severe traumatic brain injury. *Neurosurgery* 73(5): 746-52, 2013. PMID: 23863766.
 - c. Vavilala MS, Lujan SB, Qui Q, Petroni GJ, Ballarini NM, Guadagnoli N, Depetris MA, Faguaga GA, Busso LO, Garcia ME, Gonzalez Carillo OR, Medici PL, Saenz SS, Vanella EE, Fabio A, **Bell MJ**. Benchmarking Prehospital and Emergency Department Pediatric Traumatic Brain Injury Care in Argentina. *PLOS One* 11 (12): e0166478, 2016. PMID: 28005912.
 - d. Chin KH, Bell MJ, Wisniewski SR, Goundappa BGK, Kochanek PM, Beers SR, Brown SD, Adelson PD. Effect of Administration of Neuromuscular Blocking Agents in Children with Severe Traumatic Brain Injury on Acute Complication Rates and Outcomes: A Secondary Analysis from a Randomized, Controlled Trial of Therapeutic Hypothermia. *Pediatr Crit Care Med* 16(4): 352-8, 2015. PMID: 25599147.
3. *Literature from ADAPT that has already impacted clinical practice*
We have been diligent about publishing studies from ADAPT that can help to change clinical practice as the study is ongoing. Specifically, we have published data on the initial 200 subjects enrolled in ADAPT as well as characteristics of the clinical sites.
- a. Murphy S, Thomas NJ, Gertz SJ, Beca J, Luther JF, **Bell MJ**, Wisniewski SR, Hartman AL, Tasker RC. Tripartite Stratification of the Glasgow Coma Scale in Children with Severe Traumatic Brain Injury and Mortality: An Analysis from a Multicenter, Comparative Effectiveness Study. *J Neurotrauma* 2017 (in press). PMID: 28052716.
 - b. Miller Ferguson N, Sarnaik A, Miles D, Shafi N, Peters MJ, Truemper E, Vavilala MS, **Bell MJ**, Wisniewski SR, Luther JF, Hartman AL, Kochanek PM. Abusive Head Trauma and Mortality – An Analysis from an International Comparative Effectiveness Study of Children with Severe Traumatic Brain Injury. *Crit Care Med* 2017 (in press).
 - c. Kurz JE, Poloyac SM, Abend NS, Fabio A, **Bell MJ**, Wainwright MS. Variation in anticonvulsant selection and EEG monitoring following severe traumatic brain injury in children – Understanding resource availability in sites participating in a comparative effectiveness study. *Pediatr Crit Care* 17(7): 649-657, 2016. PMID: 27243415.
 - d. **Bell MJ**, Adelson PD, Hutchison JS, Kochanek PM, Tasker RC, Vavilala MS, Beers SR, Fabio A, Kelsey SF, Wisniewski SR. Differences in Medical Therapy Goals for Children with Severe Traumatic Brain Injury – An International Study. *Pediatr Crit Care Med* 14(8): 811-8, 2013. PMID: 23863819.
4. *Literature that has informed the TBI guidelines from single center*
We have performed a number of studies to inform the evidenced-based guidelines from data within a single center.
- a. Stippler, M, Ortiz V, Adelson PD, Chang Y-F, Tyler-Kabara EC, Wisniewski SR, Fink EL, Kochanek PM, Brown SD, **Bell MJ**. Brain Tissue Oxygen (PbO₂) Monitoring after Severe

- Traumatic Brain Injury in Children – Relationship to Outcome and Association with Other Clinical Parameters. *J Neurosurg Pediatr* 10(5): 383-91, 2012. PMID: 22978637.
- b. Shein SL, Ferguson NM, Kochanek PM, Bayir H, Clark RSB, Fink EL, Tyler-Kabara EC, Wisniewski SR, Tian Y, Balasubramani GK, **Bell MJ**. Effectiveness of Pharmacological Therapies for Intracranial Hypertension in Children with Severe Traumatic Brain Injury – Results from an Automated Data Collection System Time-Synched to Drug Administration. *Pediatr Crit Care Med* 17(3): 236-45, 2016. PMID: 26673840.
 - c. Ferguson NM, Shein SL, Kochanek PM, Luther J, Wisniewski SR, Clark RSB, Tyler-Kabara EC, Adelson PD, **Bell MJ**. Intracranial Hypertension and Cerebral Hypoperfusion in Children with Severe Traumatic Brain Injury: Thresholds and Burden in Accidental and Abusive Insults. *Pediatr Crit Care* 17(5): 444-50, 2016. PMID: 27028792.
 - d. Mtaweh H, Smith R, Kochanek PM, Wisniewski SR, Fabio A, Vavilala MS, Adelson PD, Toney NA, **Bell MJ**. Energy Expenditure in Children after Severe Traumatic Brain Injury. *Pediatr Crit Care* 15(3): 242-9, 2014. PMID: 24394999.
5. *The role of biomarkers for neurological injuries*
- Given the burden of illness of neurological conditions of children, I have been a leader in studying the utility of blood- and CSF-based biomarkers in children.
- a. **Bell MJ**, Adelson PD, Doughty LA, Carcillo JA, Clark RSB, DeKosky ST, Kochanek PM. Interleukin-6 and Interleukin-10 in Cerebrospinal Fluid Following Severe Traumatic Brain Injury in Children. *J Neurotrauma* 14: 451-457, 1997. PMID: 9257663.
 - b. Su E, **Bell MJ**, Kochanek PM, Wisniewski SR, Bayir H, Clark RSB, Adelson PD, Tyler-Kabara EC, Janesko-Feldman KL, Berger RP. Increased CSF Concentrations of Myelin Basic Protein after TBI in Infants and Children: Absence of Significant Effect of Therapeutic Hypothermia. *Neurocrit Care* 17(3): 401-7, 2012. PMID: 22890910.
 - c. Fink EL, Berger RP, Clark RSB, Watson RS, Angus DC, Panigrahy A, Richichi R, Callaway CW, **Bell MJ**, Monello S, Hayes RL, Kochanek PM. Exploratory Study of Serum Ubiquitin Carboxyl-Terminal Esterase L1 and Glial Fibrillary Acidic Protein for Outcome Prognostication after Pediatric Cardiac Arrest. *Resuscitation* 101: 65-70, 2016. PMID: 26855294.
 - d. Au AK, **Bell MJ**, Fink EL, Aneja RK, Kochanek PM, Clark RSB. Serum Biomarkers Predict Neurological Morbidity in Diagnostically Diverse PICU Patients. *Neurocritical Care* 2017 (in press). PMID: 28612133.

Complete List of Published Work in MyBibliography:

[http://www.ncbi.nlm.nih.gov/sites/myncbi/michael.bell.1/bibliography/47839422/public/?sort=date&direction=asc
ending](http://www.ncbi.nlm.nih.gov/sites/myncbi/michael.bell.1/bibliography/47839422/public/?sort=date&direction=ascending)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Holubkov, Richard

eRA COMMONS USER NAME (credential, e.g., agency login): RHOLUBKOV

POSITION TITLE: Professor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION		Completion Date MM/YYYY	FIELD OF STUDY
University of Chicago (Chicago, IL)	B.S.	05/1985	Statistics
Carnegie-Mellon University (Pittsburgh, PA)	M.S.	05/1986	Statistics
University of Washington (Seattle, WA)	M.S.	05/1993	Biostatistics
University of Washington (Seattle, WA)	Ph.D.	06/1995	Biostatistics

A. Personal Statement

I am a senior biostatistician and Professor in the Division of Critical Care in the Department of Pediatrics at the University of Utah School of Medicine, where I direct and co-direct Data Coordinating Centers (DCCs) for several federally and foundation-funded multicenter clinical trials and research networks. The major focus of my career has been the coordination, design and analysis of multicenter prospective cohort studies and clinical trials, particularly in the settings of pediatric critical care, cardiac surgery, and interventional cardiology. I have been involved in the Collaborative Pediatric Critical Care Research Network (CPCCRN) since its inception, including serving as alternate DCC PI for its first fifteen years. I collaborated with MPI Dr. Bell on a multicenter RCT within this network, and I am presently Co-Investigator for the network's ongoing Personalized Immunomodulation in Sepsis-Induced MODS (PRECISE) study. I have also mentored, and later collaborated with, co-Investigator Dr. Reeder on multiple registries and trials over the last decade. This, I am very experienced in all aspects of designing, managing, and analyzing multicenter trials in populations of critically ill children, and a successful track record as a (now very) senior biostatistician responsible for all DCC activities. In summary, I have the extensive experience to ensure that our Data Coordinating Center will efficiently meet the needs of this study in all aspects.

Citations exemplifying my relevant research experience:

1. VanBuren JM, Hall M, Zuppa AF, Mourani PM, Carcillo J, Dean JM, Watt K, **Holubkov R**. The Design of Nested Adaptive Clinical Trials of Multiple Organ Dysfunction Syndrome Children in a Single Study. Pediatr Crit Care Med. 2023 Jul 27. doi: 10.1097/PCC.0000000000003332. Epub ahead of print. PMID: 37498156.
2. Carcillo JA, Dean JM, **Holubkov R**, Berger J, Meert KL, Anand KJS, Zimmerman JJ, Newth CJL, Harrison R, Burr J, Willson DF, Nicholson C, Bell MJ, Berg RA, Shanley TP, Heidemann SM, Dalton H, Jenkins TL, Doctor A, Webster A, Tamburro RF; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN). Interaction Between 2 Nutraceutical Treatments and Host Immune Status in the Pediatric Critical Illness Stress-Induced Immune Suppression Comparative Effectiveness Trial. JPEN J Parenter Enteral Nutr. 2017 Nov;41(8):1325-1335. doi: 10.1177/0148607116670377. Epub 2016 Sep 22. PMCID: PMC6103642.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

- 2010 - Professor, Division of Critical Care, Department of Pediatrics, University of Utah, SLC, UT
 2005 - 2010 Associate Professor (tenured 7/2007), Division of Critical Care, Department of Pediatrics, University of Utah, Salt Lake City, UT
 2002 - 2005 Associate Professor (tenured 7/2005), Department of Family and Preventive Medicine, School of Medicine, University of Utah, Salt Lake City, UT
 1996 - 2005 Statistical Consultant, Children's Hospital of Pittsburgh, Pittsburgh, PA
 1995 - 2002 Assistant Professor, Department of Epidemiology, Graduate School of Public Health, and Division of Cardiology, School of Medicine, University of Pittsburgh, Pittsburgh, PA
 1991 - 1993 Research Assistant, Department of Neurological Surgery, University of Washington, Seattle, WA
 1988 - 1990 Research Associate, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA
 1986 - 1998 Research Specialist, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA
 1985 - 1986 Research Assistant, Department of Statistics, Carnegie-Mellon University, Pittsburgh, PA
 1984 - 1985 Statistical Programmer, National Opinion Research Center, University of Chicago, Chicago, IL

Other Experience and Professional Memberships

- 2022-2026 Member, Clinical Trials Review Study Section, Heart, Lung and Blood Initial Review Group, NHLBI
 2020- Member, Pediatric Advisory Committee, Food and Drug Administration
 2017-2020 Consultant, Pediatric Advisory Committee, Food and Drug Administration
 2017-2023 Associate Editor, *Trials*
 2013 Special Emphasis Panel, Reproductive Medicine Network, NICHD
 2012 - 2018 Data Safety Monitoring Board, RESCUE Trial of Hemofiltration, American Burn Association
 2012 - Observational Safety Monitoring Board, Genomic Research in Alpha 1 antitrypsin, NHLBI
 2011 Special Emphasis Panel, Pediatric Heart Network, NHLBI.
 2010 Special Emphasis Panel, Science Moving Toward Research Translation and Therapy, NHLBI.
 2008 - 2012 American Heart Association Epidemiology, Prevention, Outcomes and Behavior Science Peer Review Committee
 2007 - Protocol Review Committee, NHLBI Cardiothoracic Surgical Network
 2004 - 2007 Editorial Board, *Family Medicine*
 2013 - Member, International Society for Clinical Biostatistics
 1999 - *Ad hoc* reviewer: *Journal of Interventional Cardiology*, *Journal of the American College of Cardiology*, *Journal of the American Medical Association*, *Coronary Artery Disease*, *Pediatrics*, *BMC Cancer*, *Journal of Neurosurgery*, *BMC Ophthalmology*, *Clinical Trials*, *Trials*
 1995 - Member, Society for Clinical Trials
 1993 - Member, American Statistical Association

Honors

- 1990 – 1995 National Research Service Award, Traineeship in Biostatistics
 1990 – 1993 Achievement Rewards for College Scientists Fellowship
 1985 Membership, Phi Beta Kappa
 1985 – 1986 Richard King Mellon Fellowship for Graduate Study
 1981 – 1985 National Merit Scholarship, University of Chicago
 1981 – 1985 Illinois State Scholarship
 1981 – 1985 John F. Polakovic Foundation Scholarship

C. Contributions to Science

1. **Multicenter Randomized Clinical Trial Design, Management, and Analysis.** I have extensive experience as chief biostatistician for the design, development, coordination, and analysis of multicenter interventional randomized trials, free-standing as well as within research networks. Examples include a trial in the NICHD-funded Collaborative Pediatric Critical Care Research Network investigating whether nutriceuticals reduced rates of infection and sepsis among PICU-hospitalized children (**1a**), a trial in the EMSC-funded Pediatric Emergency Care Applied Research Network assessing effectiveness of dexamethasone in treating children with emergent bronchiolitis (**1b**), and the NHLBI-funded Therapeutic Hypothermia After Cardiac Arrest (THAPCA) trials examining efficacy of hypothermia versus normothermia for survival and neurobehavioral function (**1c, 1d**).
 - a. Carcillo JA, Dean JM, **Holubkov R**, et al (2012). The randomized comparative pediatric critical illness stress-induced immune suppression (CRISIS) prevention trial. *Pediatr Crit Care Med*, 13(2), 165-73. PMCID: PMC3302948
 - b. Cornelius HM, Zorc JJ, Mahajan P, Shaw KN, **Holubkov R**, et al. (2007). A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med*, 357(4), 331-9. PMID: 17652648.
 - c. Moler FW, Silverstein FS, **Holubkov R**, et al (2015). Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children. *N Engl J Med*, 372(20):1898-908. PMCID: PMC4470472
 - d. Moler FW, Silverstein FS, Holubkov R, et al (2017). Therapeutic hypothermia after in-hospital cardiac arrest in children. *N Engl J Med*, 376(4): 318-329. PMCID: PMC5310766
2. **Hydrocephalus Research.** I have applied my experience in multicenter interventional studies as PI for Data Coordinating Centers for two foundation and federally funded North American consortia assessing hydrocephalus treatment and outcomes in children (the HCRN) and in adult patients. Key HCRN publications include a sequential protocol to reduce post-shunting infection (**2a**), assessment of factors affecting acute interventional outcomes (**2b**), and initial evaluation of a promising technique termed choroid plexus cauterization that may allow selected children to avoid permanent shunts (**2c**), now being compared to shunting in an ongoing randomized trial. The adult HCRN has recently published a detailed description of etiologies and other characteristics of adults diagnosed with and treated for hydrocephalus (**2d**)
 - a. Kestle JR, **Holubkov R**, Cochrane D, et al. (2016) A new Hydrocephalus Clinical Research Network protocol to reduce cerebrospinal fluid shunt infection. *J Neurosurg Pediatr*, 17(4), 391-6. PMID: 23313978 DOI: 10.3171/2015.8.PEDS15253.
 - b. Riva-Cambrin J, Shannon CN, **Holubkov R**, et al. (2012). Center effect and other factors influencing temporization and shunting of cerebrospinal fluid in preterm infants with intraventricular hemorrhage. *J Neurosurg Pediatr*, 9(5), 473-81. PMCID: PMC3361965
 - c. Kulkarni AV, Riva-Cambrin J, Browd SR, Drake JM, **Holubkov R**, et al. (2014). Endoscopic third ventriculostomy and choroid plexus cauterization in infants with hydrocephalus: a retrospective Hydrocephalus Clinical Research Network study. *J Neurosurg Pediatr*, 14(3), 224-9. PMID: 27258593
 - d. Williams MA, Nagel SJ, Luciano MG, Relkin N, Zwimpfer TJ, Katzen H, **Holubkov R**, Moghekar A, Wisoff JH, McKhann GM, Golomb J, Edwards RJ, Hamilton MG. (2019). The clinical spectrum of hydrocephalus in adults: report of the first 517 patients of the Adult Hydrocephalus Clinical Research Network registry. *J Neurosurg*. 132(6):1773-1784. PMID: 31125971. doi: 10.3171/2019.2.JNS183538.
3. **Pediatric Critical Care Research.** As alternate PI of the CPCCRN, I have been active in research work, presenting and publishing statistically oriented materials to the critical care community on behalf of the network. One example is a detailed examination of the Data Safety Monitoring Board (DSMB)'s role in the early stopping of a CPCCRN clinical trial (**3a**). Within the CPCCRN, I have also collaborated with pediatric researchers in the development of morbidity assessments (**3b**), and determining optimal, "efficient" time intervals for assessing a child's risk profile at the time of PICU admission (**3c**). Developments from this work were used to develop predictive models for multilevel outcomes, addressed in Section 5 below.
 - a. **Holubkov R**, Casper TC, Dean JM, et al (2013). The role of the Data and Safety Monitoring Board in a clinical trial: the CRISIS study. *Pediatr Crit Care Med*, 14(4), 374-83. PMCID: PMC3648617
 - b. Pollack MM, **Holubkov R**, Glass P, et al (2009). Functional status scale: new pediatric outcome measure. *Pediatrics*, 124(1), e18-28. PMCID: PMC3191069

- c. Pollack MM, Dean JM, Butler J, **Holubkov R**, Doctor A, et al. (2013). The ideal time interval for critical care severity-of-illness assessment. *Pediatr Crit Care Med*, 14(5), 448-53. PMCID: PMC3720693
4. Interventional Cardiology Research. As a senior DCC biostatistician at the University of Pittsburgh in the 1980's and 1990's, I had the privilege of working on NHLBI-funded studies of cardiac interventions during an era when angioplasty and other catheter-based interventions were emerging as alternatives to bypass surgery for patients with extensive coronary artery disease. I was chief DCC biostatistician for key reports demonstrating improved angioplasty success rates due to increased investigator experience and technological improvements (**4a**), and chief biostatistician for the design of the Bypass Angioplasty Revascularization Investigation (BARI), which demonstrated that bypass surgery was superior to angioplasty among randomized patients with diabetes (**4b**). I subsequently directed the DCC for the international multicenter Artificial Valve Endocarditis Revascularization Investigation (AVERT) randomized trial (**4c**), which demonstrated an early risk of explant due to paravalvular leak among patients, and since coming to Utah have collaborated on various investigations of pediatric cardiac surgery approaches (**4d**).
- a. Detre K, **Holubkov R**, Kelsey S, et al (1988). Percutaneous transluminal coronary angioplasty in 1985-1986 and 1977-1981. The National Heart, Lung, and Blood Institute Registry. *N Engl J Med*, 318(5), 265-70. PMID: 2961993
- b. BARI Investigators [Writing Group of 22 including **Holubkov R**] (1997). Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing PTCA and CABG in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 96, 1761-9. PMID: 9323059
- c. Schaff H, Carrel T, Steckelberg JM, Grunkemeier GL, **Holubkov R**. (1999). Artificial Valve Endocarditis Reduction Trial (AVERT): protocol of a multicenter randomized trial. *J Heart Valve Dis*, 8(2), 131-9. PMID: 10224570.
- d. Hawkins JA, Kaza AK, Burch PT, Lambert LM, **Holubkov R**, Witte MK. (2010). Simple versus complex truncus arteriosus: neutralization of risk but with increased resource utilization. *World J Pediatr Congenit Heart Surg*, 1(3), 285-91.
5. Predictive Model Development. I have employed Classification and Regression Tree (CART) techniques to develop models predicting outcomes after head trauma (**5a**), and approaches to maximize model predictive abilities in the setting of nested two-stage studies (**5b**). As chief CC biostatistician for the EMSC-funded PECARN, I was responsible for design and analysis of a 40,000-patient prospective study using CART to identify subsets of children with traumatic brain injury for whom CT scan was not necessary, due to negligible risk of clinically significant TBI. The "decision rule" generated from this study (**5c**) is presently in the implementation phase. I have also collaborated with CPCCRN physicians in the development of a trichotomous prediction model, which simultaneously predicts risk of in-hospital mortality (effectively updating the PRISM risk stratification) and the risk of a child developing a significant new morbidity during their hospital stay (**5d**).
- a. Temkin NR, **Holubkov R**, Machamer JE, Winn HR, Dikmen SS. (1995). Classification and regression trees (CART) for prediction of function at 1 year following head trauma. *J Neurosurg*, 82(5), 764-71. PMID: 7714600
- b. Breslow NE, **Holubkov R**. (1997) Weighted likelihood, pseudo-likelihood and maximum likelihood methods for logistic regression analysis of two-stage data. *Stat Med* 16(1-3):103-16. PMID: 9004386.
- c. Kuppermann N, Holmes JF, Dayan PS, Hoyle JD Jr, Atabaki SM, **Holubkov R**, Nadel FM, et al.(2009). Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. *Lancet*, 374(9696), 1160-70. PMID: 19758692
- d. Pollack MM, **Holubkov R**, Funai T, et al. (2015). Simultaneous prediction of new morbidity, mortality, and survival without new morbidity from pediatric intensive care: a new paradigm for outcomes assessment. *Crit Care Med*, 43(8): 1699-709. PMCID: PMC4657566

Complete list of Published Work in My Bibliography:

<https://www.ncbi.nlm.nih.gov/sites/myncbi/richard.holubkov.1/bibliography/48005280/public/?sort=date&direction=ascending>

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Kudchadkar, Sapna Ravi

eRA COMMONS USER NAME (credential, e.g., agency login): sapnakudchadkar

POSITION TITLE: Associate Professor of Anesthesiology & Critical Care Medicine; Pediatrics; and Physical Medicine & Rehabilitation; Vice Chair for Pediatric Anesthesiology and Critical Care Medicine; Anesthesiologist-in-Chief, Johns Hopkins Children's Center

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Washington University in St. Louis, St. Louis, MO	B.A.	05/1999	Biochemistry and French
University of Chicago, Chicago, IL	M.D.	06/ 2003	Medicine
Johns Hopkins Hospital, Baltimore, MD	Residency	06/2006	Pediatrics
Johns Hopkins Hospital, Baltimore, MD	Residency	06/2009	Anesthesiology
Johns Hopkins Hospital, Baltimore, MD	Fellowship	06/2011	Pediatric Critical Care & Anesthesiology
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD	Ph.D.	05/2018	Clinical Investigation

A. Personal Statement

I am an Associate Professor of Anesthesiology and Critical Care Medicine (ACCM), Pediatrics, and Physical Medicine and Rehabilitation and Vice Chair of Pediatric Anesthesiology and Critical Care Medicine at the Johns Hopkins University School of Medicine. My research career focuses on critically ill children – in particular, understanding the effects of sedation optimization, sleep promotion, delirium prevention, family engagement and acute rehabilitation in the pediatric intensive care unit (PICU) setting to improve patient outcomes. As a practicing pediatric critical care physician and pediatric anesthesiologist with a PhD in Clinical Investigation from the Johns Hopkins Bloomberg School of Public Health, I am ideally equipped to bring my expertise to the training program. I have a track record of suitable training, preliminary data and publications (152 publications; 86 as first or senior author). In addition to the PICU Up! (R01HD103811) and PROXIMUS (R01DK132348) clinical trials for which I am PI, my leadership for multicenter studies has also been demonstrated in my role as the PI for the PARK-PICU Study, an international point prevalence study with >200 participating sites to evaluate the current state of acute rehabilitation practices in PICUs. I have served as the primary mentor for Dr. Anjali Garg who is a current T32 trainee as well as Dr. Jessica LaRosa who is a KL2 awardee whose research focuses in social determinants of health and safety in acute rehabilitation, respectively. Moreover, as the Vice Chair for Pediatric ACCM, I have extensive experience in mentoring students, post-doctoral fellows and junior faculty, training and supervision of research personnel, development of data tracking and management systems for multicenter trials, oversight of data analyses and syntheses, and management of project budgets.

Ongoing and recently completed projects I would like to highlight include:

R01HD103811

Kudchadkar (PI)

6/8/21-5/31/26

Clinical Effectiveness of the “PICU Up!” Multifaceted Early Mobility Intervention for Critically Ill Children: A pragmatic, stepped-wedge trial

R01DK132348

Mehta/Kudchadkar (MPI)

4/15/22-01/31/25

Protein Optimization with Exercise to Improve Muscle Mass and Functional Outcomes (PROXIMUS)

R21HD093369

Curley/Zuppa/Kudchadkar (MPI)

7/1/17-6/30/21

RESTORE resilience (R2) in Critically Ill Children

Citations I would like to highlight:

- a. LaRosa JM, Nelliot A, Zaidi M, Vaidya D, Awojoodu R, **Kudchadkar SR**. Mobilization Safety of Critically Ill Children. *Pediatrics*. 2022 Apr 1;149(4):e2021053432. PMID: 35352118.
- b. Ista E, Redivo J, Kananur P, Choong K, Colletti J, Needham DM, Awojoodu R, **Kudchadkar SR**. Assessing Pain, Both Spontaneous Awakening and Breathing Trials, Choice of Sedation, Delirium Monitoring/Management, Early Exercise/Mobility, and Family Engagement/Empowerment Bundle Practices for Critically Ill Children: An International Survey of 161 PICUs in 18 Countries. *Crit Care Med*. 2022 Jan 1;50(1):114-125. PMID: 34259659
- c. **Kudchadkar SR**, Nelliot A, Awojoodu R, Vaidya D, Traube C, Walker T, Needham DM; Prevalence of Acute Rehabilitation for Kids in the PICU (PARK-PICU) Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Physical Rehabilitation in Critically Ill Children: A Multicenter Point Prevalence Study in the United States. *Crit Care Med*. 2020 May;48(5):634-644. PMCID: PMC7539558.
- d. Wieczorek B, Ascenzi J, Kim Y, Lenker H, Potter C, Shata NJ, Mitchell L, Haut C, Berkowitz I, Pidcock F, Hoch J, Malamed C, Kravitz T, **Kudchadkar SR**. PICU Up!: Impact of a Quality Improvement Intervention to Promote Early Mobilization in Critically Ill Children. *Pediatr Crit Care Med*. 2016 Dec;17(12):e559-e566. PMCID: PMC5138131.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2018-present	Associate Professor, Departments of Anesthesiology and Critical Care Medicine, Pediatrics, and Physical Medicine and Rehabilitation, Johns Hopkins Hospital, Baltimore, MD
2011-2017	Assistant Professor, Department of Anesthesiology and Critical Care Medicine and Department of Pediatrics, Johns Hopkins Hospital, Baltimore, MD
2009-2011	Postdoctoral Fellow, Pediatric Anesthesiology and Critical Care, Johns Hopkins Hospital, Baltimore, MD
2006-2009	Resident, Anesthesiology, Johns Hopkins Hospital, Baltimore, MD
2003-2006	Resident, Pediatrics, Johns Hopkins Hospital, Baltimore, MD

Other Experience and Professional Memberships

2021	NIH Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Initiative Reviewer
2020-present	Senior Associate Editor, <i>Pediatric Critical Care Medicine</i>
2019	NIH NINDS NST-2 Committee, ad hoc reviewer
2019-present	International Advisory Board, <i>Lancet Child and Adolescent Health</i>
2019	NIH NINDS Special Emphasis Panel, ZNS1, SRB-G (23)
2017-2020	Associate Editor, <i>Pediatric Critical Care Medicine</i>
2017	NIH NINDS/NSD-K Committee, ad hoc reviewer
2007-present	Member, Society of Critical Care Medicine, Pediatric and Anesthesiology Sections

Board Certification

2014	Subspecialty Board Certification, Pediatric Anesthesiology
2012	Subspecialty Board Certification: Pediatric Critical Care Medicine
2010	Diplomate, American Board of Anesthesiology
2006	Diplomate, American Board of Pediatrics

Honors

2021	Johns Hopkins President's Frontier Research Award Finalist
2020	Fellow of the American College of Critical Care Medicine
2017-2021	Presidential Citation, Society of Critical Care Medicine
2016	Johns Hopkins Health System Clinical Collaboration and Teamwork Award
2013	Alfred Sommer Scholar Award for Outstanding Ph.D. Student in the Graduate Training Program in Clinical Investigation, Johns Hopkins Bloomberg School of Public Health

C. Contributions to Science

1. **Evaluating practice heterogeneity & knowledge gaps in sedation, sleep & delirium in pediatric ICU.** My PhD research focused on identifying the interplay between sleep, sedation and delirium in critically ill children, which led to the development of a standardized interprofessional early mobility pathway. First, I identified sleep as a critical knowledge gap in how we care for critically ill children via a rigorous systematic review. I then designed and conducted an international survey of pediatric intensivists that demonstrated: (1) substantial heterogeneity in pediatric intensive care unit (PICU) sedation, sleep promotion and delirium practices; (2) wide-spread use of sedation practices detrimental to restorative sleep; (3) lack of noise reduction and light optimization; and (4) delirium screening is rarely performed. I continued to investigate sleep promotion, including environmental factors and sedative practices, identifying alarms and monitors as an important source of noise and stress for patients and staff. I also led the publication of the first systematic review to identify characteristics of post-intensive care syndrome in critically ill children. This body of work represents foundational progress regarding sedation, delirium and sleep in critically ill infants and children.
 - a. **Kudchadkar SR**, Aljohani OA, Punjabi NM. Sleep of critically ill children in the pediatric intensive care unit: a systematic review. *Sleep Med Rev*. 2014; 18(2):103-110. PMCID: PMC3883975
 - b. Cooper-Flaigle M, Ascenzi J, **Kudchadkar SR**. Identifying barriers to delirium screening and prevention in the pediatric ICU: evaluation of PICU staff knowledge. *J Pediatr Nurs*. 2016; 31(1):81-84. PMCID: PMC4724532
 - c. **Kudchadkar SR**, Beers MC, Ascenzi JA, Jastaniah E, Punjabi NM. Nurses' perceptions of the pediatric intensive care unit environment and work experience after transition to single-patient rooms. *Am J Crit Care*. 2016; 25(5):e98-e107. PMID: 27587429
 - d. **Kudchadkar SR**, Berger J, Patel R, Barnes S, Twose C, Walker T, Mitchell R, Song J, Anton B, Punjabi NM. Non-pharmacological interventions for sleep promotion in hospitalized children. *Cochrane Database Syst Rev*. 2022 Jun 15;6(6):CD012908. PMID: 35703367; PMCID: PMC9199068.
2. **Establishing magnitude of sleep disturbance and delirium in hospitalized children and characterizing activity quantitatively in the PICU setting.** Building on my investigations identifying knowledge gaps in sleep and delirium (see above), I conducted a study that obtained objective data demonstrating severe sleep disruption in critically ill, mechanically ventilated children via use of sleep EEG. This study demonstrated the association of opioids and benzodiazepines with disorganized sleep during pediatric mechanical ventilation. Given the potential links between sleep disruption and delirium, I collaborated with colleagues to confirm a high prevalence of delirium in PICUs internationally. I followed this investigation with prospective studies of day-night patterns in children admitted to the PICU and pediatric cardiac ICU after major surgery using actigraphy. These studies demonstrated severe disruption of sleep-wake patterns and persistent immobility which persist after discharge from the PICU, identifying an urgent need for PICUs to integrate sleep, sedation, delirium and early mobility using non-pharmacologic approaches.
 - a. **Kudchadkar SR**, Yaster M, Punjabi AN, Quan SF, Goodwin JL, Easley RB, Punjabi NM. Temporal characteristics of the sleep EEG power spectrum in critically ill children. *J Clin Sleep Med*. 2015; 11(12): 1449-1454. PMCID: PMC4661338
 - b. **Kudchadkar SR**, Aljohani O, Johns J, Leroux A, Alsafi E, Jastaniah E, Gottschalk A, Shata NJ, Al-Harbi A, Gergen D, Nadkarni A, Crainiceanu C. Day-Night Activity in Hospitalized Children after Major Surgery: An Analysis of 2271 Hospital Days. *J Pediatr*. 2019 Jun;209:190-197.e1. PMCID: PMC6535352.
 - c. Traube C, Rosenberg L, Thau F, Gerber LM, Mauer EA, Seghini T, Gulati N, Taylor D, Silver G, **Kudchadkar SR**. Sleep in Hospitalized Children With Cancer: A Cross-Sectional Study. *Hosp Pediatr*. 2020 Nov;10(11):969-976. PMID: 33122175.
 - d. Gregory JL, Brown AT, **Kudchadkar SR**. Characterizing Sleep Disruption and Delirium in Children After Cardiac Surgery: A Feasibility Study. *Pediatr Crit Care Med*. 2021 Nov 1;22(11):988-992. PMCID: PMC8570973.

3. **Demonstration of the safety and feasibility of early mobilization in critically ill children using a multifaceted, interprofessional approach.** Integrating optimal approaches for sedation, sleep promotion and delirium prevention are critical for early mobilization in critically ill children. Adult critical care researchers have demonstrated the benefit of the 'ABCDEF' (Assess Pain, Both Spontaneous Awakening and Breathing Trials, Choice of Sedation, Delirium Monitoring, Early Mobility, Family Engagement) bundle for improving ICU outcomes, but similar evidence in pediatrics is limited. Therefore, I have collaborated to establish groundwork for early mobilization in critically ill children and used creative approaches to implement early rehabilitation initiatives in the PICU setting. After identifying knowledge gaps in PICU early mobility and developing and testing a multifaceted early mobility program (PICU Up!), our body of work has provided the first related evidence-based recommendations for critically ill children. Our single-center PICU Up! study established disparities in early rehabilitation for children with normal baseline function, which was confirmed in our international point prevalence studies. Additionally, our surveys of 161 PICUs across the world revealed very low rates of early mobility implementation.
- a. Wieczorek B, Burke C, Al-Harbi A, **Kudchadkar SR**. Early mobilization in the pediatric intensive care unit: a systematic review. *J Pediatr Intensive Care*. 2015;4(4):129-170. PMCID: PMC4568750
 - b. Wieczorek B, Ascenzi J, Kim Y, Lenker H, Potter C, Shata NJ, Mitchell L, Haut C, Berkowitz I, Pidcock F, Hoch J, Malamed M, Kravitz T, **Kudchadkar SR**. PICU Up!: Impact of a quality improvement intervention to promote early mobilization in critically ill children. *Pediatr Crit Care Med*. 2016; 17(12): e559-e566. PMCID: PMC5138131
 - c. **Kudchadkar SR**, Nelliot A, Awojoodu R, Vaidya D, Traube C, Walker T, Needham DM. Physical rehabilitation in critically ill children: a multicenter point prevalence study in the United States. *Crit Care Med*. 2020 May;48(5):634-644. PMCID: PMC7539558.
 - d. Ista E, Redivo J, Kananur P, Choong K, Colletti J, Needham DM, Awojoodu R, **Kudchadkar SR**. ABCDEF Bundle Practices for Critically Ill Children: An international survey of 161 pediatric intensive care units in 18 countries. *Crit Care Med*. 2021 Jul 13. Epub ahead of print. PMID: 34259659.
4. **Functional measurement of mobility in the ICU across a wide spectrum of age and baseline function.** With successful implementation and dissemination of a nurse-driven early mobility pathway, I identified an urgent need to develop pediatric-specific tools for measuring physical function and progression in the critical care environment. I brought together a team of physical and occupational therapists across the pediatric and adult hospital settings to validate the Activity Measure for Post-Acute Care (AM-PAC) in the pediatric acute care setting. We also capitalized on our robust point prevalence data to translate the Johns Hopkins Highest Level of Mobility (JH-HLM) tools to the pediatric inpatient population.
- a. Miura S, Wieczorek B, Lenker H, **Kudchadkar SR**. Normal baseline function is associated with delayed rehabilitation in critically ill children. *J Intensive Care Med*. 2020 Apr;35(4):405-410. PMCID: PMC7288243.
 - b. Young D, **Kudchadkar SR**, Friedman M, Lavezza A, Kumble S, Daley K, Flanagan E, Hoyer E. Using Systematic Functional Measurements in the Acute Hospital Setting to Combat the Immobility Harm. *Arch Phys Med Rehabil*. 2020 Dec 26:S0003-9993(20)31340-X. PMID: 33373600.
 - c. Hosey MM, Needham DM, **Kudchadkar SR**. Fatigue in critical care survivors: multidisciplinary and self-management strategies. *Anaesthesia*. 2021 Sep;76(9):1163-1166. PMID: 33878209.
 - d. Denlinger K, Young DL, Beier M, Friedman M, Quinn J, **Kudchadkar SR**. Psychometric Testing of the Activity Measure for Post-Acute Care (AM-PAC) in the Pediatric Acute Care Setting. *Pediatric Physical Therapy* 2021 Jul 1;33(3):149-154. PMID: 34086622.

Complete List of Published Work in MyBibliography (152 publications: 86 as first or senior author):
<https://www.ncbi.nlm.nih.gov/myncbi/sapna.kudchadkar.1/bibliography/public/>

BIOGRAPHICAL SKETCH

NAME: Paquette, Erin

eRA COMMONS USER NAME (credential, e.g., agency login): etalati

POSITION TITLE: Associate Professor (Pediatrics and Law by Courtesy)

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Northwestern University, Evanston, IL	BA	06/2001	Biology & Science in Human Culture
University of Pennsylvania School of Medicine, Philadelphia, PA	MD	05/2007	Medicine
University of Pennsylvania School of Medicine, Philadelphia, PA	MA	05/2007	Bioethics
University of Pennsylvania Law School, Philadelphia, PA	JD	05/2007	Law
University of Chicago Comer Children's Hospital, Chicago, IL	Resident	06/2010	Pediatrics
Dana Farber Cancer Institute, Boston, MA	Postdoctoral Fellow	06/2013	Center for Population Sciences
Boston Children's Hospital/Harvard Medical School, Boston, MA	Fellow	06/2013	Pediatric Critical Care
American Bar Foundation/JPB Foundation, Chicago , IL	Other training	08/2021	Access to Justice Scholar
National Institutes of Health, NICHD, University of Utah, Salt Lake City, UT	NIH training grant K12	12/2024	Pediatric Critical Care and Trauma Scientist Development Program
National Institutes of Health National Institute for Child Health and Development/Northwestern University/Ann & Robert H. Lurie Children's Hospital, Chicago, IL	NIH training grant K23	07/2024	Career development award

A. Personal Statement

I am the Director of Clinical and Organizational Ethics, Chair of the Ethics Advisory Board, Co-Chair of Equity of Care on the President's Council for Equity, Diversity, and Inclusion, and a member of the steering committee for the Health Equity and Antiracism Center at Ann & Robert H. Lurie Children's Hospital, co-founder and co-lead of the Social Determinants of Health Subgroup of the Pediatric Acute Lung Injury and Sepsis Investigators Network, a member of the Pediatric Emergency Care Applied Research Network Health Disparities Working Group, an appointed member of the Society of Critical Care Medicine Ethics Committee and the Society of Pediatric Research Advocacy Committee, an elected Director at Large for the American Society of Bioethics Board of Directors, Associate Professor of Pediatrics (Critical Care) at the Northwestern University Feinberg School of Medicine and Associate Professor of Law (by courtesy) at the Northwestern University Pritzker School of Law. I bring 16 years of experience as a scholar in bioethics, educator, investigator and consultant at three institutions on matters of clinical, organizational, and research ethics, as well as more than 20 years' experience in education, research, service and leadership in matters related to health disparities and promotion of health equity and social justice. My primary areas of scholarly work include (1) assessing and addressing inequities in research engagement and retention of diverse groups; (2) understanding and addressing barriers to inclusion of underrepresented voices in ethical discourse; and (3) addressing social influencers of health through education and direct service.

My expertise in research ethics and equity has led to multiple scholarly, advisory and educational endeavors stemming from a more than 20-year interest in these intersecting areas. I authored a law review article on recourse for violations of research ethics values in the global context and have co-authored several manuscripts related to research ethics including an article on research ethics consultation services, a book chapter on the ethics of community engaged research, and articles on the importance of engaging diverse populations in research and overcoming barriers related to the trustworthiness of researchers. As a mixed

quantitative and qualitative methods researcher, I have studied the ethics of engagement of diverse populations in research and assessing and addressing informed consent and assent in the research process, including development and validation of a new metric to assess comprehension in research. My research has been funded by the National Institute for Child Health and Development, Health Resources and Services Administration, and the American Bar Foundation as an Access to Justice Scholar. I have co-developed several videos to improve equity in research through health literacy focused educational videos related to the research process. I have served as a consultant/expert and member in several roles related to research ethics, including as a member of Harvard Catalyst Research Ethics Working Group, a member of the joint Lurie-Northwestern IRB, as the ethics representative on 4 data safety and monitoring boards (DSMBs), an appointed member of the National Heart, Lung and Blood Institute DSMB, and as a research ethics and equity expert consultant for the Northwestern CTSA supported Clinical Research Ethics and Equity Consultation Service. Additionally, as Director of Clinical and Organizational Ethics, I have addressed issues related to ethics and equity in the clinical context. This experience will augment approaches in the research context.

My combined expertise and interdisciplinary professional training in law, medicine, and ethics situate me to be an effective contributor to both ethics and equity considerations of the OPTICOM project. Specifically, I will assist the research team in planning an equity conscious recruitment plan mindful of historical injustices and inequities in pain assessment and management for minoritized groups. Additionally, I will participate in ongoing monitoring of enrollment of diverse populations in this randomized study to aim for an equitable enrollment pattern, and to advise the research team on strategies to engage difficult to reach populations if enrollment remains inequitable.

Ongoing and recently completed projects that I would like to highlight include:

- NIH NICHD K12HD047349 Keenan (PI) 01/01/2019 - 12/31/23 Predictors of Enrollment of Racially and Ethnically Diverse Participants in Emergency and Critical Care Research
 - Health Resources and Services Administration 6UH1HP29963-03-01 Persell (PI) 07/01/2018 - 06/30/2022 National Collaborative for Education to Address the Social Determinants of Health
 - American Bar Foundation/JPB Foundation Paquette (PI) 06/01/2020 - 08/31/2022 A Foundation for Justice? A 360 Assessment of Outcomes from Participation in a Medical Legal Partnership
 - NIH NICHD 1K23HD09828901A1 Paquette (PI) 08/01/2020-07/31/2024 Adapt to Engage: Assessing for Disparities and Potential Targets for Intervention to Engage Acutely Ill Children in Research
 - Patient Centered Outcomes Research Institute Michelson and Lindau (PIs) 01/31/2023 - 01/30/2028 The Missing Pieces Trial: A Multi-Site Pragmatic Comparative Effectiveness Trial of Interventions to Support Parents After Their Child's Unexpected or Traumatic Death
1. Taylor HA, Porter KM, Paquette ET, McCormick JB, Tumilty E, Arnold JF, Spector-Bagdady K, Danis M, Brandt D, Shah J, Wilfond BS, Lee LM. Creating a Research Ethics Consultation Service: Issues to Consider. *Ethics Hum Res.* 2021 Sep;43(5):18-25. PubMed Central PMCID: PMC9254506.
 2. Paquette ET, Derrington S. Deconstructing Trust and Recognizing Vulnerability in Research With Diverse Populations. *Am J Bioeth.* 2018 Apr;18(4):37-39. PubMed PMID: 29621455.
 3. Paquette ET, Ross L. The Challenges of Incorporating Research Ethics Consultation Into Institutional Human Subjects Protections Programs. *Am J Bioeth.* 2018 Jan;18(1):49-51. PubMed Central PMCID: PMC6214683.
 4. Paquette E, Najita J, Morley D, Joffe S. Child and Parent Understanding of Clinical Trials: The Semi-Structured Comprehension Interview. *AJOB Empirical Bioethics.* 2015; 6(2):23-32.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

- 2023 - Editorial Board Member, Pediatric Critical Care Medicine
2023 - Co Editor-in-Chief, Journal of Health Advocacy
2023 - Data Safety and Monitoring Board Ethics Representative, National Heart, Lung, and Blood Institute
2022 - Associate Professor of Law (Courtesy), Northwestern University Pritzker School of Law, Chicago, IL

- 2022 - Associate Professor, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL
- 2022 - Ethics Expert, DSMB, Epinephrine Dosing Study, Boston Children's Hospital/Harvard University, Boston, MA
- 2022 - Early Career NIH Reviewer, National Institutes of Health, Bethesda, MD
- 2022 - Ethics Committee Member, Society of Critical Care Medicine, Mount Prospect, IL
- 2022 - Board of Directors, American Society of Bioethics and Medical Humanities, Mount Prospect, IL
- 2022 - Advocacy Committee Member, Society for Pediatric Research, The Woodlands, TX
- 2020 - Chair, Ethics Advisory Board, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL
- 2020 - Co-Chair, Equity of Care, President's Council for Equity, Diversity and Inclusion, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL
- 2020 - Director for Clinical and Organizational Ethics, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL
- 2019 - 2022 Assistant Professor of Law (courtesy), Northwestern University Pritzker School of Law, Chicago, IL
- 2018 - Ethics Representative, DSMB, Autism Connecting the Dots Study, Drexel University, Philadelphia, PA
- 2018 - 2020 Co-Chair, Equitable Care, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL
- 2016 - Ethics Representative, Genetic and Metabolic Diseases Advisory Committee, Illinois Department of Public Health, Chicago, IL
- 2016 - 2022 Assistant Professor, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL
- 2016 - 2020 Associate Chair, Ethics Advisory Board, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL
- 2015 - 2019 Adjunct Professor, Northwestern University School of Law MSL Program, Chicago, IL
- 2013 - Attending Physician, Division of Pediatric Critical Care, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL
- 2013 - 2015 Instructor of Pediatrics, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL
- 2012 - 2013 Chief Fellow, Div of Pediatric Critical Care Medicine, Dept of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA

Honors

- 2019 - 2024 Pediatric Critical Care and Trauma Scientist Scholar, University of Utah
- 2022 - 2023 Grenvik Family Award for Excellence in Ethics, Society of Critical Care Medicine
- 2021 - 2022 Departmental Leadership Award, Ann & Robert H Lurie Children's Hospital of Chicago
- 2020 - 2021 Inaugural Access to Justice Scholar, American Bar Foundation
- 2018 - 2019 Public Voices Fellow/Op-Ed Project, Northwestern University
- 2016 - 2018 Extramural Recipient, National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Human Development Pediatric Extramural Loan Repayment Program
- 2012 - 2013 Chief Fellow, Div of Pediatric Critical Care, Dept of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital and Department of Anesthesia, Harvard Medical School
- 2012 - 2012 Appointed Ethics Associate, Boston Children's Hospital
- 2012 - 2012 Trainee Travel Award, Boston Children's Hospital Alumni Council
- 2010 - 2010 Senior Resident of the Year, University of Chicago Comer Children's Hospital
- 2010 - 2010 Gary C. Comer Award for Professional Excellence, Univ of Chicago Comer Children's Hospital
- 2008 - 2008 Intern of the Year, University of Chicago Comer Children's Hospital
- 2007 - 2007 Outstanding Clinical Student Award, Clinical Legal Educators Association
- 2007 - 2007 Cum Laude Graduate, University of Pennsylvania Law School
- 2006 - 2006 Pro Bono Challenge Award, Latham & Watkins, LLP
- 2005 - 2005 Elaine Osborne Jacobson Award, Pound Civil Justice Institute
- 2001 - 2001 Departmental Honors, Department of Science & Human Culture, Northwestern University

2021	Affiliated Scholar, American Bar Foundation
2021	Alpha Omega Alpha Faculty Inductee, Northwestern University

C. Contribution to Science

1. **Expertise in empirical research related to bioethical issues including quantitative, qualitative, and mixed-methods, psychometric development and assessment, and review of datasets.** My work has included a variety of clinical and research contexts including reactions to treatment refusals in pediatrics (cited below). I have also had experience in the development of psychometric instruments including the Semi-structured comprehension interview (key reference above) and the Multi-dimensional Illness Severity Questionnaire to measure illness impact (MISQ below). I have employed survey methods to assess brain death practices (cited below), child and parent understanding of clinical research (key reference) and barriers and motivators to research engagement (key reference). I have used mixed methods to assess perspectives on biorepository enrollment (key reference). I have experience with retrospective dataset studies including evaluating sociodemographic associations with biorepository enrollment (forthcoming manuscript under minor revisions and forthcoming manuscripts on enrollment of diverse populations in research). Finally, I have experience with methods to conduct rigorous scoping reviews and qualitative studies (MLP manuscript cited below).
 - a. Mataya L, Ross LF, Ghavam A, Paquette ET. Pediatric Intensivist and Pediatric Neurologist Perspectives and Practices on Death by Neurologic Criteria. *J Clin Ethics.* 2021 Fall;32(3):195-205. PubMed Central PMCID: PMC9275594.
 - b. Gard LA, Bartell T, Shah AK, Setrini AB, Sheehan K, Miller CH, Paquette ET. Interprofessional Education in Medical-Legal Partnerships (MLPs) to Address Social Determinants of Health. *J Health Care Poor Underserved.* 2021;32(4):1720-1733. PubMed PMID: 34803038.
 - c. Paquette ET, Joffe S. The Multidimensional Illness Severity Questionnaire: Preliminary evaluation of a brief parent-reported measure of illness severity. *J Paediatr Child Health.* 2019 Oct;55(10):1241-1246. PubMed PMID: 30723995.
 - d. Talati ED, Lang CW, Ross LF. Reactions of pediatricians to refusals of medical treatment for minors. *J Adolesc Health.* 2010 Aug;47(2):126-32. PubMed PMID: 20638004.
2. **Ethical Foundations for Research and Consent in Vulnerable Populations.** Understanding the conceptual foundations for ethical research and consent is fundamental to the practice of medicine and research. In a law review article on informed consent in research, An Open Door To Ending Exploitation: Accountability for Violations of Informed Consent Under the Alien Tort Statute, I cultivated my interest in consent and heightened my desire to acquire research skills to inform rational approaches to consent in research. In more recent work, I have considered ethical dilemmas and complexities in the conduct of research, such as the limits of confidentiality between investigator and research participant, what constitutes acceptable risk in research, how research ethics consultation services can be useful in ensuring ethical research and the importance of engaging diverse populations in research. My long term career goals include the translation of evidence into practice and policy, relevant to the proposed work to utilize evidence related to participation of groups affected by health disparities in research to advance policy in this area.
 - a. Foster CC, Paquette ET. Improving Advance Care Planning for Seriously Ill Children: Engaging a Diverse Research Population Early and Often. *J Pediatr.* 2021 Feb;229:16-18. PubMed Central PMCID: PMC8480434.
 - b. Paquette ET, Shah SK. Towards Identifying an Upper Limit of Risk: A Persistent Area of Controversy in Research Ethics. *Perspect Biol Med.* 2020;63(2):327-345. PubMed PMID: 33416656.
 - c. Paquette ET, Ross L. The Challenges of Incorporating Research Ethics Consultation Into Institutional Human Subjects Protections Programs. *Am J Bioeth.* 2018 Jan;18(1):49-51. PubMed Central PMCID: PMC6214683.
 - d. Paquette ET, Ross LF. Consent Is the Cornerstone of Ethically Valid Research: Ethical Issues in Recontacting Subjects Who Enrolled in Research as a Minor. *Am J Bioeth.* 2015;15(10):61-3. PubMed PMID: 26479111.
3. **Neuroethics.** I have developed empirical and conceptual work around the ethics of disorders of consciousness and brain death. I have specifically explored controversies in brain death determination and declaration including variation in practices around determination and declaration, whether consent should

- be required for conducting the brain death evaluation, and factors relating to refusal of the brain death evaluation and declaration.
- a. Rissman L, Paquette ET. Ethical and legal considerations related to disorders of consciousness. *Curr Opin Pediatr.* 2020 Dec;32(6):765-771. PubMed Central PMCID: PMC8204725.
 - b. Truog RD, Paquette ET, Tasker RC. Understanding Brain Death. *JAMA.* 2020 Jun 2;323(21):2139-2140. PubMed PMID: 32356868.
 - c. Paquette E, Frader J, Shah S, C Tasker R, Truog R. Beyond the Apnea Test: An Argument to Broaden the Requirement for Consent to the Entire Brain Death Evaluation. *Am J Bioeth.* 2020 Jun;20(6):17-19. PubMed PMID: 32441597.
 - d. Leemputte M, Paquette E. Consent for Conducting Evaluations to Determine Death by Neurologic Criteria: A Legally Permissible and Ethically Required Approach to Addressing Current Controversies. *Current Pediatrics Reports.* 2019 December; 7(4):152.
- 4. Ethical and equitable decision making and practice for children, particularly vulnerable children, including critically ill children and those at risk for abuse and neglect.** I have written about the need to evaluate for neighborhood and person-level characteristics that may place critically ill children at a disadvantage for equitable care. I have explored issues for children suspected to have suffered abusive head trauma and decision-making standards for those living in non-intimate families, in addition to assessing the goals of the best interest standard generally. I have examined the adequacy of health care surrogacy laws for children. Additionally, I have discussed the role of minors in medical decision making, particularly in the setting of treatment refusals.
- a. Paquette ET. Reckoning With Redlining and Other Structural Barriers to Health of Critically Ill Children: Addressing Systemic Racism Will Require Shifting the Focus From Micro- to Macrolevel Analysis of Social Risks. *Pediatr Crit Care Med.* 2022 Aug 1;23(8):662-665. PubMed Central PMCID: PMC9523488.
 - b. Derrington SF, Magee P, Paquette ET. Restoring Justice: Affluence Should Not Determine Children's Access to Critical Care Services. *Pediatr Crit Care Med.* 2021 Dec 1;22(12):1097-1099. PubMed Central PMCID: PMC8647763.
 - c. Paquette E. Constrained Parental Autonomy and the Interests of Children in Non-Intimate Families. *J Clin Ethics.* 2019 Fall;30(3):218-222. PubMed PMID: 31573965.
 - d. Lang A, Paquette ET. Involving Minors in Medical Decision Making: Understanding Ethical Issues in Assent and Refusal of Care by Minors. *Semin Neurol.* 2018 Oct;38(5):533-538. PubMed PMID: 30321891.
- 5. Public Health Ethics.** In the setting of the pandemic, I explored pediatric specific obligations and considerations in the public health setting. I described the role of children's hospitals in alleviating strain on the health care system, including ethical foundations for this obligation and reasons for suboptimal execution of these duties. I evaluated ethical considerations for vaccine mandates in children. Finally, I described how shared decision making, the ideal approach for decision making in the pediatric population may be impacted by public health considerations during a public health emergency.
- a. Kolaitis IN, Fry JT, Paquette ET. How Suboptimal Consolidation of Care During the COVID-19 Pandemic Can Teach Us to Do Better. *Hosp Pediatr.* 2021 Aug;11(8):e156-e158. PubMed Central PMCID: PMC8336455.
 - b. Paquette ET. In the Wake of a Pandemic: Revisiting School Approaches to Nonmedical Exemptions to Mandatory Vaccination in the US. *J Pediatr.* 2021 Apr;231:17-23. PubMed Central PMCID: PMC7816863.
 - c. Patel A, Feltman DM, Paquette ET. Integrating Public Health Ethics into Shared Decision Making for Children During the Novel Coronavirus Disease-19 Pandemic. *J Pediatr.* 2021 Apr;231:259-264. PubMed Central PMCID: PMC7706416.
 - d. Paquette ET, Derrington S, Fry JT, Michelson K, Patel A, Shah S, Frader JE. Shifting Duties of Children's Hospitals During the COVID-19 Pandemic. *J Hosp Med.* 2020 Oct;15(10):631-633. PubMed Central PMCID: PMC7531940.

Complete List of Published Work in My Bibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/erin.paquette.1/bibliography/public/>

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Howell, Joy D.

eRA COMMONS USER NAME (credential, e.g., agency login): JOYHOWELL

POSITION TITLE: Professor of Clinical Pediatrics

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Sophie Davis School of Biomedical Education	BS	05/93	Premedical Studies
Children's Hospital of Philadelphia	Resident	06/98	Pediatrics
New York Presbyterian Hospital	Fellow	06/01	Pediatric Critical Care

A. Personal Statement

I am a Professor of Clinical Pediatrics and former Program Director of the Pediatric Critical Care Medicine (PCCM) Fellowship program at Weill Cornell Medicine (WCM). Additionally, I hold roles as Vice Chair for Diversity in Pediatrics and Assistant Dean for Diversity and Student Life. I have been committed to clinical excellence and the education and development of trainees for the entirety of my career.

I have taught and mentored many students, residents, and fellows at WCM, New York Presbyterian (NYP) Cornell and Queens, and Memorial Sloan Kettering Cancer Center. After serving as Co-Director of the Fellowship Program from 2005-2007, I served as PCCM Fellowship Program Director from 2007-2020. My responsibilities included the enrichment and delivery of the PCCM curriculum as well as the recruitment, selection, training, and evaluation of PCCM fellows. Over that 15-year period, I had ample opportunity to support and nurture fellows, residents, and students at the respective stages of their professional development. My passion for education resulted in my being honored by the pediatric house staff with the “Excellence in Teaching Award” both in 2006 and 2010 and the Excellence in Medical Education Award for medical student education in 2019.

In 2017 I was invited to serve as the inaugural Vice Chair for Diversity in the Department of Pediatrics. I lead the efforts to advance compositional diversity, inclusion excellence, and equity within the department of pediatrics. In partnership with colleagues within and outside of Pediatrics, I have led several initiatives that address diversity and promote inclusion at the student, resident, staff, and faculty levels. Beyond Cornell, I have been invited to organize and lead competitive workshops at national meetings including the Association of American Medical Colleges Group on Diversity and Inclusion and, in the pediatric community at the Pediatric Academic Societies annual meetings. My work within the Department of Pediatrics afforded me the opportunity to be a candidate and ultimately the individual selected to serve the institution as Assistant Dean for Diversity and Student Life (ADDL).

As Assistant Dean for Diversity and Student Life, I oversee the operations of the Office of Student Diversity along with my counterpart in the Graduate School, interact with and support the professional development of underrepresented and minority students, consult and deliver Diversity, Equity, and Inclusion (DEI) - specific curricular content to medical students. My experience as an educator and DEI advocate as well as my prior experience leading capacity-building programs with my clinical experiences uniquely positions me to advise and oversee on the Plan for Enhancing Diverse Perspectives, including minimization of implicit bias to ensure enrollment of a diverse clinical population in collaboration with Dr. Chani Traube and the OPTICOM Leadership team.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021- present	Professor of Clinical Pediatrics, Weill Cornell Medicine
2020 -present	Assistant Dean of Diversity and Student Life, Weill Cornell Medicine
2020 – present	Director, Travelers Summer Research Fellowship Program
2017- present	Vice Chair for Diversity in Pediatrics, Weill Cornell Medicine
2007- 2020	Director, Pediatric Critical Care Medicine Fellowship, New York Presbyterian Hospital, Weill Cornell Campus
2005-2007	Co-Director, Pediatric Critical Care Medicine Fellowship, New York Presbyterian Hospital, Weill Cornell Campus
2007-2021	Associate Professor of Clinical Pediatrics, Weill Cornell Medical College, New York Presbyterian Hospital
2001-2008	Assistant Professor of Pediatrics, Weill Cornell Medical College, New York Presbyterian Hospital
2001-2007	Director, Pediatric Intensive Care Unit, New York Hospital of Queens

Other Experience and Professional Memberships

2011- Present	Fellow, American College of Critical Care Medicine
2009- 2011	President, New York Society of Pediatric Critical Care Medicine
2007- 2009	Vice President, New York Society of Pediatric Critical Care Medicine
2003- Present	Fellow, American Academy of Pediatrics
1999- 2003	Member, American College of Chest Physicians
1998- Present	Member, New York Society of Pediatric Critical Care Medicine
1998- Present	Member, Society of Critical Care Medicine
1995- Present	Member, American Academy of Pediatrics

Honors

2020	Co-Chair Society of Critical Care Medicine Annual Congress
2019	Excellence in Medical Education Award, Weill Medical College of Cornell University
2017-2021	Presidential Citation Award, Society of Critical Care Medicine
2012	Physician of the Year, Department of Nursing NYP/WCM
2010	Award for Teaching Excellence, Department of Pediatrics, Weill Cornell Medicine
2006	Award for Teaching Excellence, Department of Pediatrics, Weill Cornell Medicine

C. Contributions to Science

1. Pediatric Critical Care Simulation Education. My primary role is that of a clinician-educator. As such, the majority of my nonclinical efforts have been focused on the administration and curricular enhancement of the Pediatric Critical Care Medicine Fellowship and the education of fellows, residents, medical students, nurses, and physician assistants. In collaboration with nursing and physician colleagues, I led the development and implementation of an *in situ* interdisciplinary simulation program that has been in place for the past eleven years; I directed this program for the first eight years of its existence. This work represented a significant enhancement to the fellowship curriculum and overall program quality as simulation education evolved into a standard of education. The products of these administrative and teaching responsibilities include the following publications and abstracts.

- a. Howell J.D., Greenwald BM. Breathing New Life into PALS Training. *Pediatr Crit Care Med.* 2014 Mar;42(3):744-5. PMID: 24534968
- b. Nellis ME, Howell J.D., Ching K, Bylund C. The Use of Simulation to Improve Resident Communication and Personal Experience at End-of-Life Care. *J Ped Int Care* 2017; 6 (2): 91-97. PMID: 31073430 PMCID: PMC6260254

- c. Goodman DM, Winkler MK, Fiser RT, Abd-Allah S, et. al. The Accreditation Council for Graduate Medical Education proposed work hour regulations. *Pediatr Crit Care Med.* 2011 Jan;12(1):120-1. PMID: 21209582
 - d. Bergman C, **Howell J.** Critical Cardiopulmonary Event Series: Four Simulations for Pediatric ICU Fellows, Critical Care Nurses, and Pediatric Residents. MedEdPortal March 2020. PMID: 32342011 PMCID: PMC7182043
2. **Pediatric Oncology Care.** Although pediatric oncology patients are often treated within multidisciplinary pediatric intensive care units, critically ill children with cancer may represent a distinct cohort with specific patterns of disease and in turn require management customized for the oncology population. Our research has investigated variables that impact outcomes following surgical resection of neuroblastoma as well as the severity and complexity of illness in children who have undergone bone marrow transplantation. Our findings suggest that patients who had longer operative times and received less fluid intraoperatively following resection of neuroblastoma were more likely to require vasoactive medications as part of their care in the postoperative period. The following publications highlight the need for studies specific to critically ill pediatric oncology patients.
- a. Ross SL, Greenwald BM, **Howell J.D.**, Pon S, Rutigliano D.N., Spicyn N, LaQuaglia M.P., Outcomes following thoracoabdominal resection of neuroblastoma. *Critical Care Medicine* 2009; 37(9): 2625-31. PMID: 19451841
 - b. **Howell J.D.**, Kutko M.C., Greenwald B.M. Oncology patients in the pediatric intensive care unit: It's time for prospective study. *Pediatr Crit Care Med.* 2011 Oct; 12(6):680-1. PMID: 22067817
 - c. Hsing D.D., **Howell J.D.**, Greenwald BM. The critically ill pediatric hematopoietic stem cell transplant patient: what have we learned? *Pediatr Crit Care Med.* 2013 Mar;14(3):326-8. PMID: 23462355
3. **Multi-institutional Quality Collaboration.** In addition to significant teaching delivered to pediatric residents and fellows and medical students, I participate as site principal investigator in a multiinstitutional quality improvement collaborative that seeks to identify risk factors for tracheal intubation-associated adverse events. Members of the collaborative contribute prospectively collected data from their center and in turn analyze data within the entire database to identify and disseminate emerging best practices for endotracheal intubation in children. I have served as a secondary author on our manuscript that characterizes medications used for tracheal intubation in children and have been a contributing author on other publications.
- a. Tarquinio KM1, **Howell J.D.**, Montgomery V, Turner D.A., Hsing D.D., Parker M.M., Brown C.A. 3rd, Walls RM, Nadkarni V.M., Nishisaki A; for the National Emergency Airway Registry for Children and Pediatric Acute Lung Injury and Sepsis Investigators Network. Current Medication Practice and Tracheal Intubation Safety Outcomes from a Prospective Multicenter Observational Cohort Study. *Pediatr Crit Care Med.* 2015 Mar;16(3):210-8. PMID: 25581629
- Collaborative Contributions:
- b. Li S, Rehder KJ, Giuliano J.S. Jr, Apkon M, Kamat P. National Emergency Airway Registry for Children (NEAR4KIDS) Investigators; Pediatric Acute Lung Injury and Sepsis Investigator PALISI Network Investigators. Development of a Quality Improvement Bundle to Reduce Tracheal Intubation-Associated Events in Pediatric ICUs. *Am J Med Qual.* 2016 Jan-Feb;31(1):47-55. PMID: 25143411
 - c. Sanders R.C. Jr, Nett ST, Davis K.F., Parker M.M., Bysani G.K. National Emergency Airway Registry for Children NEAR4KIDS Investigators; Pediatric Acute Lung Injury and Sepsis Investigators Network. Family Presence During Pediatric Tracheal Intubations. *JAMA Pediatrics.* 2016 March; 170 (3): e154627. PMID: 26954533
 - d. Grunwell J.R., Kamat P.P., Miksa M., Krishna A., Walson K., Simon D., Krawiec C., Breuer R., Lee J.H., Gradidge E., Tarquinio K., Shenoi A., Shults J., Nadkarni V., Nishisaki A.; National Emergency Airway Registry for Children (NEAR4KIDS) and the Pediatric Acute Lung Injury and

Sepsis (PALISI) Network. Trend and Outcomes of Video Laryngoscope Use Across PICUs. *Pediatr Crit Care Med.* 2017 Aug;18(8):741-749. PMID: 28492404 PMCID: PMC6317345.

4. **Equity, Diversity, and Inclusion in Pediatrics.** As Vice Chair for Diversity in Pediatrics, in collaboration with many, I lead the department's efforts surrounding Diversity, Inclusion Excellence and Equity. Since my appointment, I have participated in local and national education around implicit bias, healthcare disparities, and diversity in healthcare.

- a. Killinger J.S., Greenwald B.M., **Howell J.D.** The Needle Is Not Moving. *Pediatr Crit Care Med.* 2020. October; 21(10): 898-899. PMID: 33009298
- b. Sotto-Santiago S., Poll-Hunter N., Trice T, Buenconsejo-Lum L, Golden S, **Howell J.**, Jacobs N., Lee W., Mason H., Ogunyemi D., Crespo W., Lamba S. A Framework for Develo PMID: 34469355. ping Antiracist Medical Educators and Practitioner-Scholars. *Acad Med.* 2021 Aug 31.

Complete List of Published Work in My Bibliography:

<https://pubmed.ncbi.nlm.nih.gov/?term=howell%20joy>

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Vanessa N. Madrigal

ERA COMMONS USER NAME (credential, e.g., agency login): VAMADRIGAL

POSITION TITLE: Associate Professor, George Washington University School of Medicine, Washington DC; Pediatric Critical Care Medicine Attending at Children's National Health System, Washington DC

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Kent State University, Kent, OH	BA	05/2000	English Literature
Wright State University School of Medicine, Dayton, OH	MD	05/2004	Medicine
University of Pennsylvania, Philadelphia, PA	MSCE	12/2017	Master of Science in Clinical Epidemiology (Conc. In Bioethics)
Children's Mercy Hospital, Kansas City, MO	Certificate	05/2019	Pediatric Bioethics

A. Personal Statement

The study leadership has built an impressive roster of qualified researchers to contribute to this work. I am honored, and enthusiastic in joining the effort. While completing a Masters of Science in Clinical Epidemiology (with a concentration in bioethics) from the University of Pennsylvania, I have attained rigorous scientific background of methods in design, implementation and analysis in clinical research, in addition to necessary background in bioethics. Recently I rounded out this education with a certificate in Pediatric Bioethics from Children's Mercy Hospital in Kansas City which included training in Pediatric Research Ethics. At Children's National Hospital, as the Director of the Pediatric Ethics Program, I serve as the Research Subject Advocate, provide Research Ethics Consultation, and am a member of our Responsible Conduct of Research education committee providing robust monthly curriculum for members of our community. I am working to expand the clinical ethics consult service and education curriculum for all trainees, faculty, and staff and serve as the research subject advocate.

This background has given me the ability to give a meaningful contribution to this and other projects and particularly with regards to research ethics and diversity. I am dedicated to the proposed research have commitment from my division in support of pursing this exciting opportunity. My role in the proposed grant would be to provide ethics leadership and expertise to ensure diverse perspective are represented in the following ways: 1) evaluate approach to address and mitigate implicit bias 2) evaluate education and suggested best practices for the multistep PEDP (Plan for enhancing Diverse Perspectives) in support of enrolling a diverse population throughout the study 3) assist in monitoring enhance compositional diversity of enrollees and 4) provide a personal perspective representation a Latin / Hispanic background.

Ongoing and recently completed projects that I would like to highlight include:

1R01NR015831

Hinds (PI), Role: Co-Investigator

09/29/2015-06/30/2019

How Parent Constructs Affect Parent and Family Well-Being after a Child's Death.

RO1 NR012026 – 02S1

Feudtner (PI), Role: Co-Investigator

10/01/2011-9/30/2012

Bioethics Supplement to Decision-making in Pediatric Advanced Care

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments:

2023-present	Chair, Pediatric Ethics Affinity Group for American Society for Bioethics and Humanities
2022-2023	Co-Chair, Pediatric Ethics Affinity Group for American Society for Bioethics and Humanities
2021-present:	Associate Professor, George Washington University School of Medicine
2019 – present	Director, Ethics Program and Chair of the Clinical Ethics Committee
2014-2021:	Assistant Professor, George Washington University School of Medicine
2014-present:	Pediatric Critical Care Medicine Attending at Children's National Medical Center
2013-2014:	Assistant Professor, University of Pennsylvania, Perelman School of Medicine, Department of Anesthesiology and Critical Care Medicine
2010-2014:	Pediatric Critical Care Medicine Attending at Children's Hospital of Philadelphia
2010-2013:	Instructor, University of Pennsylvania, Perelman School of Medicine, Department of Anesthesiology and Critical Care Medicine
2007-2010:	Pediatric Critical Care Medicine Fellowship, The Children's Hospital of Philadelphia, Philadelphia, PA
2004-2007:	Pediatric Residency, Miami Children's Hospital, Miami, FL

Honors:

2022	Elda Arce Teaching Scholar Award
2014	HPI Safety Summit. Safety Cinema Award: Most Creative
2011, 2014	CHOP Faculty Teaching Honor Roll
2006	Luis Felipe Mencia, MD Award in Pediatric Surgery
2003	Lilian Pauyo Scholarship
2002	Paul Ambrose Health Promotion Leadership Symposium and Scholarship
2002-2004	Joseph Collins Foundation Scholarship
2000-2002	Ohio Board of Regents Graduate/Professional Fellowship
2000	Magna Cum Laude and University Honors
2000	Chester E. Finn Scholarship
1999	W. Leslie Garnett Scholarship
1996-2000	Oscar Ritchie Memorial Scholarship
1996	Kent State University Honors College Scholarship

C. Contributions to Science

1. My early research focused primarily on the ethics issue of parental decision-making, the desire for autonomy and guidance and factors that influence those experiences when in the Pediatric Intensive Care Unit (PICU) environment. Parents as surrogate decisions-makers are known to be under enormous amounts of stress and experience a vast and complex range of emotions. We investigated how emotions played into those decisions and how parents have a vast range of preferences on how they make decisions, and what type of support they require. We completed an RCT that investigated outcomes related to the implementation of a Pediatric continuity care intensivist, a role that grew out of the need to increase continuity, communication and consistency for long-stay patients in the PICU. More recently...ethics

- a. **Madrigal VN**, Carroll KW, Hexem KR, Faerber JA, Morrison WE, Feudtner C. Parental DecisionMaking Preferences in the Pediatric Intensive Care Unit. *Critical Care Medicine* 2012 October;40(10):2876-2882. PMID: 22824932
 - b. **Madrigal VN**, Carroll KW, Faerber JA, Walter JK, Morrison WE, Feudtner C. Parental Sources of Support and Guidance When Making Difficult Decisions in the Pediatric Intensive Care Unit. *The Journal of Pediatrics* 2016 Feb;169:221-226.e4. PMID: 26651432
 - c. **Madrigal VN**, Kelly KP. Supporting Family Decision-making for a Child Who Is Seriously Ill: Creating Synchrony and Connection. *Pediatrics*. 2018 Nov;142(Suppl 3):S170-S177. PMID: 30385624 PMCID: PMC6220653
 - d. **Madrigal V**, Walter JK, Sachs E, Himebauch AS, Kubis S, Feudtner C. Pediatric continuity care intensivist: A randomized controlled trial. *Contemp Clin Trials*. 2019 Jan;76:72-78. PMID: 30468772
2. As a local and national leader in ethics, I am also dedicated to issues of health inequity, addressing racism and understanding the role and strategies to mitigate bias. I have written on the role of ethics consultants when addressing racism, and examining the effects of decisions in cases of medical complexity in addition to research ethics in neonatal cardiac care.
 - a. Shapiro JP, Anspacher M, **Madrigal V**, Lantos JD. Disposition Decisions in Cases of Medical Complexity and Health Inequity. *Pediatrics*. 2022 Aug 1:150(2): e2021055558. doi: 10.1542/peds.2021055558.
 - b. **Madrigal VN**, Feltman DM, Leuthner SR, Kirsch R, Hamilton R, Dokken D, Needle J, Boss R, Lelkes E, Carter B, Macias E, Bhombal S. Bioethics for Neonatal Cardiac Care. *Pediatrics*. 2022 Nov 1:150(Suppl 2):e2022056415N. doi: 10.1542/peds.2022-056415N. PMID: 36317974
 - c. **Madrigal V**, MacDuffie K, Paquette ET. Addressing Racism in the Healthcare Encounter: The Role of Clinical Ethics Consultants. *J Clin Ethics*. 2022;33(3):202-209. PMID: 36137202
 3. As a co-investigator, I have contributed to the advancement of knowledge in decision-making in the areas of family centered rounds, tracheostomy discussions, the chronically critically ill, long-stay patients and communication training for trainees. I've also contributed to a systematic review of benefits and burdens and as an active member of the International PARK-PICU Investigator team. These areas address issues on decision-making, best practices and how multiple factors can influence outcomes on decisions regarding clinical care and research.
 - a. Herbert LM, Watson AC, **Madrigal, VN**, October TW. Discussing Benefits and Risks of Tracheostomy: What Physicians Actually Say. *Pediatric Crit Care Med*. 2017 Dec;18(12):e592-e597. PMID: 28938289 PMCID: PMC5716895
 - b. Weaver MS, Mooney-Doyle K, Kelly KP, Montgomery K, Newman AR, Fortney CA, Bell CJ, Spruit JL, Kurtz Uveges M, Wiener L, Schmidt CM, **Madrigal VN**, Hinds PS. The Benefits and Burdens of Pediatric Palliative Care and End-of-Life Research: A Systematic Review. *J Palliat Med*. 2019 March 5. doi: 10.1089/jpm.2018.0483. PMID: 30835596 PMCID: PMC6755658
 - c. Ista, E., Redivo, J., Kananur, P., Choong, K., Colletti, J., Jr, Needham, D. M., Awojoodu, R., Kudchadkar, S. R., & International PARK-PICU Investigators (2022). ABCDEF Bundle Practices for Critically Ill Children: An International Survey of 161 PICUs in 18 Countries. *Critical care medicine*, 50(1), 114–125.doi: 10.1097/CCM.0000000000005168. PMID: 34259659
 - d. Edwards JD, Wocial LD, **Madrigal VN**, Moon MM, Ramey-Hunt C, Walter JK, Baird JD, Leland BD. Continuity Strategies for Long-Stay PICU Patients: Consensus Statements From the Lucile Packard Foundation PICU Continuity Panel. *Pediatric Critical Care Medicine* 2023 October;24(10).

Complete List of Published Work in My Bibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/vanessa.madrigal.2/bibliography/public/>

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Reeder, Ron W.

eRA COMMONS USER NAME (credential, e.g., agency login): reeder

POSITION TITLE: Associate Professor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Brigham Young University, Provo, Utah	BS	12/2006	Education, Mathematics
University of Utah, Salt Lake City, Utah	MS	09/2011	Applied Math
University of Utah, Salt Lake City, Utah	PhD	12/2011	Statistics

A. Personal Statement

My role in this proposal is Co-investigator. I will write the statistical analysis plan, direct and oversee all analyses, and personally carry out more advanced analyses. I am well qualified to direct all biostatistical efforts of the Utah Coordinating Center in support of the proposed research.

I have been the principal investigator for the Pediatric Colorectal and Pelvic Learning Consortium (PCPLC) Coordinating Center since inception in 2016 and for the Children's Hospital Of Philadelphia Statistical Investigation Core (CHOPSTIC) since inception in 2021. I was also coordinating center principal investigator for the "Improving outcomes from pediatric cardiac arrest" trial (5R01HL131544-05) and "Validation of physiologic CPR quality using non-invasive waveform analytics" (5R01HL147616-03) from initiation in 2016 and 2018, respectively, through completion in 2022.

I directed the project management, data management, and statistical support of the Coordinating Center for 21 multicenter studies across 4 networks including the Collaborative Pediatric Critical Care Research Network (CPCCRN; 5U01HD049934-15), "Helping to End Addiction Long-term" (HEAL; 3U24TR001597-06S1), Hydrocephalus clinical research network (HCRN), and Pediatric Colorectal and Pelvic Learning Consortium (PCPLC). We provided project management, institutional review board (IRB) support, study training, and site monitoring. We facilitated regular meetings with investigators and research personnel to provide ongoing training and support with discussions of 'lessons learned', etc. We built, maintained, and validated secure, web-based data capture systems, ensuring that data were logical, consistent, and complete; and we provided full statistical support from inception through publication and dissemination of results. Throughout these projects, I partnered with more than a hundred investigators from dozens of institutions to support efficient, high-quality clinical research.

Citations I would like to highlight (from my ongoing collaboration with the Children's Hospital of Philadelphia resuscitation science team):

1. Sutton RM, Wolfe HA, **Reeder RW**, Ahmed T, Bishop R, Bochkoris M, Burns C, Diddle JW, Federman M, Fernandez R, Franzon D, Frazier AH, Friess SH, Graham K, Hehir D, Horvat CM, Huard LL, Landis WP, Maa T, Manga A, Morgan RW, Nadkarni VM, Naim MY, Palmer CA, Schneiter C, Sharron MP, Siems A, Srivastava N, Tabbutt S, Tilford B, Viteri S, Bell MJ, Carcillo JA, Carpenter TC, Dean JM, Fink EL, Hall M, McQuillen PS, Meert KL, Mourani PM, Notterman D, Pollack MM, Sapru A, Wessel D, Yates AR, Zuppa AF, Berg RA. Effect of Physiologic Point-of-Care Cardiopulmonary Resuscitation Training on Survival With Favorable Neurologic Outcome in Cardiac Arrest in Pediatric ICUs: A Randomized Clinical Trial. JAMA. 2022 Mar;327(10):934-945. PMCID: PMC8905390.
2. Morgan RW, **Reeder RW**, Meert KL, Telford R, Yates AR, Berger JT, Graham K, Landis WP, Kilbaugh TJ, Newth CJ, Carcillo JA, McQuillen PS, Harrison RE, Moler FW, Pollack MM, Carpenter TC, Notterman D, Holubkov R, Dean JM, Nadkarni VM, Berg RA, Sutton RM. Survival and hemodynamics during pediatric cardiopulmonary resuscitation for bradycardia and poor perfusion versus pulseless cardiac arrest. Crit Care Med. 2020 Jun;48(6):881-889. PMCID: PMC7895327.

3. Berg RA, Morgan RW, **Reeder RW**, Tageldin A, Bell MJ, Bishop R, Bochkoris M, Burns C, Carcillo JA, Carpenter TC, Dean JM, Diddle JW, Federman M, Fernandez R, Fink EL, Franzon D, Frazier AH, Friess SH, Graham K, Hall M, Hehir DA, Horvat CM, Huard LL, Maa T, Manga A, McQuillen PS, Meert KL, Mourani PM, Nadkarni VM, Naim MY, Notterman D, Palmer CA, Pollack MM, Sapru A, Schneiter C, Sharron M, Srivastava N, Tabbutt S, Tilford B, Viteri S, Wessel D, Wolfe HA, Yates AR, Zuppa AF, Sutton RM. Diastolic blood pressure threshold during pediatric cardiopulmonary resuscitation and survival outcomes: a multicenter validation study. *Crit Care Med.* 2023 Jan 1;51(1):91-102. PMCID: PMC9970166.
4. Morgan RW, Berg RA, **Reeder RW**, Carpenter TC, Franzon D, Frazier AH, Graham K, Meert KL, Nadkarni VM, Naim MY, Tilford B, Wolfe HA, Yates AR, Sutton RM; ICU-RESUS and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network Investigator Groups. The physiologic response to epinephrine and pediatric cardiopulmonary resuscitation outcomes. *Crit Care.* 2023 Mar 13;27(1):105. PMCID: PMC10012560.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-present	Associate Professor, Division of Critical Care, Department of Pediatrics, University of Utah, Salt Lake City, Utah
2021-present	Adjunct Associate Professor, Department of Mathematics, College of Science, University of Utah, Salt Lake City, UT
2021-present	Adjunct Associate Professor, Division of Public Health, Department of Family and Preventive Medicine, University of Utah, Salt Lake City, Utah
2020-present	Board Member, Get With The Guidelines-Resuscitation Pediatric Research Task Force, American Heart Association
2019-2021	Adjunct Assistant Professor, Division of Public Health, Department of Family and Preventive Medicine, University of Utah, Salt Lake City, Utah
2016-present	Member, Steering Committee, Pediatric Colorectal and Pelvic Learning Consortium (PCPLC)
2016-present	Member, Executive Committee, Pediatric Colorectal and Pelvic Learning Consortium (PCPLC)
2016-2018	Secretary, Utah Chapter, American Statistical Association
2015-2021	Assistant Professor, Division of Pediatric Critical Care, Department of Pediatrics, University of Utah, Salt Lake City, Utah
2015-2021	Adjunct Assistant Professor, Department of Mathematics, College of Science, University of Utah, Salt Lake City, UT
2014-2015	Associate Instructor, Department of Mathematics, College of Science, University of Utah, Salt Lake City, UT
2013-present	Coordinator, Statistical Methods Seminar Series, Division of Pediatric Critical Care, Department of Pediatrics
2013-2015	Biostatistician III, Division of Pediatric Critical Care, Department of Pediatrics, University of Utah, Salt Lake City, UT
2011-2013	Biostatistician, Actavis, Inc., Salt Lake City, UT
2008-2011	Teaching Fellow, Department of Mathematics, College of Science, University of Utah, Salt Lake City, UT
2007	Software Intern, Idaho Technology, Salt Lake City, UT

Honors

2022	Star Research Achievement Award, Society of Critical Care Medicine
2019	Star Research Achievement Award, Society of Critical Care Medicine
2018	Bronze Medal Award, Society of Critical Care Medicine
2016	Star Research Achievement Award, Society of Critical Care Medicine
2011	Best Statistics Presentation, Intermountain Graduate Research Symposium, Utah State University, Logan, UT
2011	Research Fellowship, National Science Foundation and University of Utah, Salt Lake City, UT
2010	Outstanding Graduate Student Award, Department of Mathematics, University of Utah, Salt Lake City, UT
2010	Research Fellowship, National Science Foundation and University of Utah, Salt Lake City, UT

C. Contribution to Science

1. **Founded a consortium of 16 institutions to study rare diseases:** In 2016, I partnered with investigators at 5 institutions and founded a research consortium to improve the health and quality of life for individuals affected by colorectal conditions or congenital pelvic anomalies. The Pediatric Colorectal and Pelvic Learning Consortium (PCPLC) has grown to include 16 institutions. Serving on the Executive and Steering Committees, I use my background as a statistician and experience directing the efforts of the Coordinating Center to inform the priorities and direction of the consortium. As principal investigator for the Coordinating Center, I direct the project management, data management, and the statistical design and analysis for all consortium projects. I led the development of bylaws, procedures for proposing and developing new projects and manuscripts, and authorship guidelines. Under my direction, the Coordinating Center established subcommittees and facilitates their ongoing collaboration to drive the efforts of the consortium in their specific domains, allowing site investigators to contribute to rapid advancement of knowledge. The PCPLC registry now includes more than 3,000 subjects, allowing investigators to collaboratively study rare diseases including Hirschsprung disease and anorectal malformations.
 - a. **Reeder RW**, Wood RJ, Avansino JR, Levitt MA, Durham MM, Sutcliffe J, Midrio P, Calkins CM, de Blaauw I, Dickie BH, Rollins MD; Pediatric Colorectal and Pelvic Learning Consortium (PCPLC). The Pediatric Colorectal and Pelvic Learning Consortium (PCPLC): rationale, infrastructure, and initial steps. *Tech Coloproctol.* 2018 May;22(5):395-399. Epub 2018 May 4. PMID: 29725784.
 - b. Halloran DR, Smith CA, Fuller MK, Durhm MM, Dickie B, Avansino JR, Tirrell TF, Vandewalle R, **Reeder R**, Drake KR, Bates DG, Rollins MD, Levitt MA, Wood RJ; Pediatric Colorectal and Pelvic Learning Consortium. Measure twice and cut once: Comparing endoscopy and 3D cloacogram for the common channel and urethral measurements in patients with cloacal malformations. *J Pediatr Surg.* 2020 Feb;55(2):257-260. doi: 10.1016/j.jpedsurg.2019.10.045. Epub 2019 Nov 5. PMID: 31784103.
 - c. Baxter KJ, Garza JM, Rollins MD, Drake K, **Reeder RW**, Wood R, Avansino J, Calkins CM, Ralls M, Garvey EM, Durham MM; Pediatric Colorectal and Pelvic Learning Consortium (PCPLC). Multi-institutional review of bowel management strategies in children with anorectal malformations. *J Pediatr Surg.* 2020 Dec;55(12):2752-2757. doi: 10.1016/j.jpedsurg.2020.04.023. Epub 2020 May 13. PMID: 32616413.
 - d. Kastenberg ZJ, Taylor MA, Durham MM, Calkins CM, Rentea RM, Wood RJ, Avansino JR, Levitt MA, van Leeuwen KD, Lewis KE, **Reeder RW**, Rollins MD. Perioperative and long-term functional outcomes of neonatal versus delayed primary endorectal pull-through for children with Hirschsprung disease: A pediatric colorectal and pelvic learning consortium study. *J Pediatr Surg.* 2021 Aug;56(8):1465-1469. doi: 10.1016/j.jpedsurg.2021.04.024. Epub 2021 Apr 30. PMID: 34052005.
2. **Designed novel cluster-randomized trial to achieve aims with constrained resources:** I directed the biostatistical efforts of the Collaborative Pediatric Critical Care Research Network (CPCCRN) for the Pediatric Intensive Care Quality of CPR (PICqCPR) study. We demonstrated that achieving an average diastolic blood pressure of ≥ 25 mmHg during CPR in infants and ≥ 30 mmHg in children (≥ 1 year of age) was associated with increased survival. The Pediatric Advance Life Support (PALS) guidelines incorporated this in their recommendations, citing our work. I later designed and implemented a novel hybrid between a stepped-wedge and a parallel cluster randomized trial. This never-before-implemented design allowed the trial to achieve aims 9 months sooner and with 15% fewer participants than traditional designs. During enrollment, we identified independent research questions for 35 proposed manuscripts. I implemented a process for the Coordinating Center to collaborate with 81 investigators across more than a dozen institutions to efficiently plan and conduct these analyses. Within 9 months of ending enrollment, analyses, tables, and figures for all 35 manuscripts were complete. Primary aims of the trial were published in JAMA 11 months after enrollment ended.
 - a. **Berg, R.A., R.M. Sutton, R.W. Reeder**, J.T. Berger, C.J. Newth, J.A. Carcillo, P.S. McQuillen, K.L. Meert, A.R. Yates, R.E. Harrison, F.W. Moler, M.M. Pollack, T.C. Carpenter, D.L. Wessel, T.L. Jenkins, D.A. Notterman, R. Holubkov, R.F. Tamburro, J.M. Dean, and **V.M. Nadkarni**, Association Between Diastolic Blood Pressure During Pediatric In-Hospital Cardiopulmonary Resuscitation and Survival. *Circulation.* 2018. 137(17): p. 1784-1795. PMCID: PMC5916041.

- b. **Sutton, R.M., R.W. Reeder**, W. Landis, K.L. Meert, A.R. Yates, J.T. Berger, C.J. Newth, J.A. Carcillo, P.S. McQuillen, R.E. Harrison, F.W. Moler, M.M. Pollack, T.C. Carpenter, D.A. Notterman, R. Holubkov, J.M. Dean, **V.M. Nadkarni**, and **R.A. Berg**, Chest compression rates and pediatric in-hospital cardiac arrest survival outcomes. *Resuscitation*, 2018. 130: p. 159-166. PMCID: PMC6170369.
 - c. **Sutton, R.M., R.W. Reeder**, W.P. Landis, K.L. Meert, A.R. Yates, R.W. Morgan, J.T. Berger, C.J. Newth, J.A. Carcillo, P.S. McQuillen, R.E. Harrison, F.W. Moler, M.M. Pollack, T.C. Carpenter, D.A. Notterman, R. Holubkov, J.M. Dean, **V.M. Nadkarni**, and **R.A. Berg**, Ventilation Rates and Pediatric In-Hospital Cardiac Arrest Survival Outcomes. *Crit Care Med*, 2019. 47(11): p. 1627-1636. PMCID: PMC7898415.
 - d. **Reeder, R.W.**, A. Girling, H. Wolfe, R. Holubkov, R.A. Berg, M.Y. Naim, K.L. Meert, B. Tilford, J.A. Carcillo, M. Hamilton, M. Bochkoris, M. Hall, T. Maa, A.R. Yates, A. Sapru, R. Kelly, M. Federman, J. Michael Dean, P.S. McQuillen, D. Franzon, M.M. Pollack, A. Siems, J. Diddle, D.L. Wessel, P.M. Mourani, C. Zebuhr, R. Bishop, S. Friess, C. Burns, S. Viteri, D.A. Hehir, R. Whitney Coleman, T.L. Jenkins, D.A. Notterman, R.F. Tamburro, and **R.M. Sutton**, Improving outcomes after pediatric cardiac arrest - the ICU-Resuscitation Project: study protocol for a randomized controlled trial. *Trials*, 2018. 19(1): p. 213. PMCID: PMC5883604.
3. Identified three inflammation phenotypes in pediatric septic shock and demonstrated substantial long-term morbidity. I directed the project management, data management, and biostatistical support for two multicenter, observational cohort studies of pediatric sepsis. In the first, we demonstrated that one third of children surviving community-acquired septic shock remain substantially below their pre-illness health-related quality of life 12 months after their hospitalization. We further showed that duration and severity of organ dysfunction, maximum vasoactive inotropic support, and the occurrence of an acute pathological neurologic sign/event were independently associated with mortality or persistent, serious deterioration of health-related quality of life. These findings will move the field forward because by characterizing long-term changes in health-related quality of life after pediatric sepsis, future research can be designed utilizing health-related quality of life as a patient-centered outcome measure. In the second, we demonstrated that three inflammation phenotypes (immunoparalysis, thrombotic microangiopathy driven thrombocytopenia, and sequential liver failure) were associated with increased macrophage activation syndrome and mortality. Identification of pediatric sepsis phenotypes is important because it will allow more personalized treatment of sepsis.
- a. Carcillo, J.A., R.A. Berg, D. Wessel, M. Pollack, K. Meert, M. Hall, C. Newth, J.C. Lin, A. Doctor, T. Shanley, T. Cornell, R.E. Harrison, A.F. Zuppa, **R.W. Reeder**, R. Banks, J.A. Kellum, R. Holubkov, D.A. Notterman, and J.M. Dean, A Multicenter Network Assessment of Three Inflammation Phenotypes in Pediatric Sepsis-Induced Multiple Organ Failure. *Pediatr Crit Care Med*, 2019. 20(12): p. 1137-1146. PMCID: PMC8121153.
 - b. Carcillo, J.A., E.S. Halstead, M.W. Hall, T.C. Nguyen, **R. Reeder**, R. Aneja, B. Shakoory, and D. Simon, Three Hypothetical Inflammation Pathobiology Phenotypes and Pediatric Sepsis-Induced Multiple Organ Failure Outcome. *Pediatr Crit Care Med*, 2017. 18(6): p. 513-523. PMCID: PMC5457354.
 - c. Zimmerman, J.J., R. Banks, R.A. Berg, A. Zuppa, C.J. Newth, D. Wessel, M.M. Pollack, K.L. Meert, M.W. Hall, M. Quasney, A. Sapru, J.A. Carcillo, P.S. McQuillen, P.M. Mourani, H. Wong, R. Chima, A. Doctor, D. Willson, R. Holubkov, W. Coleman, S. Sorenson, J.W. Varni, J. McGilliard, W. Haaland, K. Whitlock, J.M. Dean, and **R.W. Reeder**, Trajectory of Mortality and Health Related Quality of Life Morbidity Following Community-Acquired Pediatric Septic Shock. *Critical Care Medicine*, PMCID: PMC7164680
 - d. Zimmerman, J.J., R. Banks, R.A. Berg, A. Zuppa, C.J. Newth, D. Wessel, M.M. Pollack, K.L. Meert, M.W. Hall, M. Quasney, A. Sapru, J.A. Carcillo, P.S. McQuillen, P.M. Mourani, H. Wong, R. Chima, A. Doctor, D. Willson, R. Holubkov, W. Coleman, S. Sorenson, J.W. Varni, J. McGilliard, W. Haaland, K. Whitlock, J.M. Dean, and **R.W. Reeder**, Critical Illness Factors Associated With Long-Term Mortality and Health Related Quality of Life Morbidity Following Community-Acquired Pediatric Septic Shock. *Critical Care Medicine*, PMCID: PMC7089387.

4. Developed statistical testing procedures for high-frequency data: In collaboration with my research team, I developed new methods for analyzing high-frequency data using a version of principal component analysis appropriate for curves. Near-continuous measurement of a variable over time produces a curve of measurements vs. time. Each data point along the curve provides a small amount of information, but the high correlation and sometimes irregular measurement intervals make classical analytical methods infeasible. Treating these data as curves rather than as individual points allowed us to develop statistical testing procedures suitable for this type of data. We proved the validity of our testing procedures mathematically for large sample sizes and also demonstrated their usefulness empirically for smaller sample sizes. This type of data is prevalent from many sources, making the methods we developed applicable to a wide range of disciplines. This research has been published in influential statistics, economics, and mathematics journals, including the *Journal of the Royal Statistical Society*.
- a. Horváth L, **Reeder R.** linear models. J Multivar Anal. 2012;111(C):310-334.
 - b. Horváth L, **Reeder R.** A Test of Significance in Functional Quadratic Regression. Bernoulli. 2013;19(5a):2120-2151.
 - c. Hörmann S, Horváth L, **Reeder R.** A functional version of the ARCH model. Econ Theory. 2013;29(2):267-288.
 - d. Horváth L, Kokoszka P, **Reeder R.** Estimation of the mean of functional time series and a two-sample problem. J R Stat Soc Series B Stat Methodol. 2012;75(1):103-122.

Complete List of Published Work in MyBibliography

<https://www.ncbi.nlm.nih.gov/myncbi/ron.william.reeder.1/bibliography/public/>

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Joan and Sanford I Weill Medical College

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Chani		Traube		PD/PI	212,100.00	3			53,025.00	17,233.00	70,258.00
2 . Dr.	Joy	Deanna	Howell		Co-Investigator	212,100.00	0.24			4,242.00	1,379.00	5,621.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	75,879.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Program Manager	9			86,814.00	28,215.00	115,029.00
1	Administrative Specialist	3			13,181.00	4,284.00	17,465.00
1	Grant Manager	2.4			24,880.00	8,086.00	32,966.00
1	Research Coordinator	9			53,840.00	17,498.00	71,338.00
4	Total Number Other Personnel					Total Other Personnel	236,798.00
						Total Salary, Wages and Fringe Benefits (A+B)	312,677.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium

Organization: Joan and Sanford I Weill Medical College

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

97,500.00

2. Foreign Travel Costs

Total Travel Cost _____

97,500.00

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium

Organization: Joan and Sanford I Weill Medical College

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	
2. Publication Costs	0.00
3. Consultant Services	10,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	1,503,861.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	670,856.00
	Total Other Direct Costs
	2,184,717.00

G. Direct Costs	Funds Requested (\$)*
	Total Direct Costs (A thru F)
	2,594,894.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	69.5	924,303.00	642,392.00
	Total Indirect Costs			
	642,392.00			
Cognizant Federal Agency	DHHS, Louis Martilliotti, 212-264-0918			
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
	Total Direct and Indirect Institutional Costs (G + H)
	3,237,286.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	3,237,286.00

L. Budget Justification*	File Name: Budget Justification_Final.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Joan and Sanford I Weill Medical College

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Chani		Traube		PD/PI	212,100.00	3			53,025.00	17,233.00	70,258.00
2 . Dr.	Joy	Deanna	Howell		Co-Investigator	212,100.00	0.24			4,242.00	1,379.00	5,621.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	75,879.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Program Manager	9			89,419.00	29,061.00	118,480.00
1	Administrative Specialist	3			13,181.00	4,284.00	17,465.00
1	Grant Manager	2.4			24,880.00	8,086.00	32,966.00
1	Research Coordinator	6			35,894.00	11,665.00	47,559.00
4	Total Number Other Personnel				Total Other Personnel		216,470.00
					Total Salary, Wages and Fringe Benefits (A+B)		292,349.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium

Organization: Joan and Sanford I Weill Medical College

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

60,000.00

2. Foreign Travel Costs

Total Travel Cost _____

60,000.00

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium

Organization: Joan and Sanford I Weill Medical College

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	
2. Publication Costs	0.00
3. Consultant Services	10,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	1,297,495.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	912,440.00
Total Other Direct Costs	2,219,935.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	2,572,284.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		69.5	389,519.00	270,717.00
Cognizant Federal Agency	DHHS, Louis Martilliotti, 212-264-0918			
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	2,843,001.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	2,843,001.00

L. Budget Justification*	File Name: Budget Justification_Final.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Joan and Sanford I Weill Medical College

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Chani		Traube		PD/PI	212,100.00	3			53,025.00	17,233.00	70,258.00
2 . Dr.	Joy	Deanna	Howell		Co-Investigator	212,100.00	0.24			4,242.00	1,379.00	5,621.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	75,879.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Program Manager	9			89,419.00	29,061.00	118,480.00
1	Administrative Specialist	3			13,181.00	4,284.00	17,465.00
1	Grant Manager	2.4			24,880.00	8,086.00	32,966.00
1	Research Coordinator	6			35,894.00	11,665.00	47,559.00
4	Total Number Other Personnel					Total Other Personnel	216,470.00
						Total Salary, Wages and Fringe Benefits (A+B)	292,349.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium

Organization: Joan and Sanford I Weill Medical College

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	<hr/>
	Total Equipment

Additional Equipment: File Name:

D. Travel

	Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	60,000.00
2. Foreign Travel Costs	<hr/>
	Total Travel Cost

E. Participant/Trainee Support Costs

	Funds Requested (\$)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	<hr/>
Number of Participants/Trainees	Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium

Organization: Joan and Sanford I Weill Medical College

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	
2. Publication Costs	3,000.00
3. Consultant Services	10,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	1,306,189.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	906,440.00
Total Other Direct Costs	2,225,629.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	2,577,978.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	69.5	390,789.00	271,600.00
	Total Indirect Costs			
Cognizant Federal Agency	DHHS, Louis Martilliotti, 212-264-0918			
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	2,849,578.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	2,849,578.00

L. Budget Justification*	File Name: Budget Justification_Final.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Joan and Sanford I Weill Medical College

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Chani		Traube		PD/PI	212,100.00	3			53,025.00	17,233.00	70,258.00
2 . Dr.	Joy	Deanna	Howell		Co-Investigator	212,100.00	0.24			4,242.00	1,379.00	5,621.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	75,879.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Program Manager	9			89,419.00	29,061.00	118,480.00
1	Administrative Specialist	3			13,181.00	4,284.00	17,465.00
1	Grant Manager	2.4			24,880.00	8,086.00	32,966.00
1	Research Coordinator	6			35,894.00	11,665.00	47,559.00
4	Total Number Other Personnel					Total Other Personnel	216,470.00
						Total Salary, Wages and Fringe Benefits (A+B)	292,349.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium

Organization: Joan and Sanford I Weill Medical College

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

60,000.00

2. Foreign Travel Costs

Total Travel Cost _____

60,000.00

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium

Organization: Joan and Sanford I Weill Medical College

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	
2. Publication Costs	6,000.00
3. Consultant Services	10,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	1,302,641.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	906,440.00
Total Other Direct Costs	2,225,081.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	2,577,430.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	69.5	393,789.00	273,685.00
	Total Indirect Costs			
Cognizant Federal Agency	DHHS, Louis Martilliotti, 212-264-0918			
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	2,851,115.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	2,851,115.00

L. Budget Justification*	File Name: Budget Justification_Final.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Joan and Sanford I Weill Medical College

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Chani		Traube		PD/PI	212,100.00	3			53,025.00	17,233.00	70,258.00
2 . Dr.	Joy	Deanna	Howell		Co-Investigator	212,100.00	0.24			4,242.00	1,379.00	5,621.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	75,879.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Program Manager	9			89,419.00	29,061.00	118,480.00
1	Administrative Specialist	3			13,181.00	4,284.00	17,465.00
1	Grant Manager	2.4			24,880.00	8,086.00	32,966.00
1	Research Coordinator	6			35,894.00	11,665.00	47,559.00
4	Total Number Other Personnel					Total Other Personnel	216,470.00
						Total Salary, Wages and Fringe Benefits (A+B)	292,349.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium

Organization: Joan and Sanford I Weill Medical College

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	<hr/>
	Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*	
60,000.00	
Total Travel Cost	60,000.00

E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees	Total Participant Trainee Support Costs
	<hr/>

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

UEI*: YNT8TCJH8FQ8

Budget Type*: Project Subaward/Consortium

Organization: Joan and Sanford I Weill Medical College

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	
2. Publication Costs	27,000.00
3. Consultant Services	10,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	1,311,483.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	870,440.00
Total Other Direct Costs	2,218,923.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	2,571,272.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		69.5	414,789.00	288,280.00
Cognizant Federal Agency	DHHS, Louis Martilliotti, 212-264-0918			
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	2,859,552.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	2,859,552.00

L. Budget Justification*	File Name: Budget Justification_Final.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

BUDGET JUSTIFICATION WEILL CORNELL MEDICINE

Senior/Key Personnel

Chani Traube, MD, Principal Investigator, MPI (3.00 calendar months requested) is the Director of Clinical Research Mentoring in the Department of Pediatrics and Professor of Pediatrics in the Division of Critical Care Medicine at Weill Cornell Medicine. She also serves as the Steering Committee Chair for the Collaborative Pediatric Critical Care Research Network (CPCCRN), a multicenter program devoted to development and execution of large clinical trials to investigate the safety and efficacy of treatment management strategies used for the care of critically ill and injured children. Dr. Traube has extensive experience leading multi-site studies, including investigating the relationship between the pharmacokinetics of sedatives and delirium. Her expertise in operationalizing studies in the complex PICU environment, and long history of successfully directing multi-disciplinary collaborative teams, positions her to efficiently and effectively lead this study. Dr. Traube will oversee all aspects of experimental design, clinical sites, data collection, data interpretation and analysis, study team organization, and manuscript preparation. Dr. Traube's base salary exceeds the current NIH salary cap; therefore, for purposes of this application, calendar months are calculated using the current cap of \$212,100.

Joy Howell, MD, Co-investigator (0.24 calendar months requested) is Assistant Dean for Diversity and Student Life at Weill Cornell Medicine, Vice Chair for Diversity in the Department of Pediatrics, and Professor of Clinical Pediatrics at Weill Cornell Medicine. Dr. Howell will oversee and advise on the Plan for Enhancing Diverse Perspectives, including minimization of implicit bias to ensure enrollment of a diverse clinical population. Dr. Howell's base salary exceeds the current NIH salary cap; therefore, for purposes of this application, calendar months are calculated using the current cap of \$212,100.

Other Personnel

Carolyn Weinbaum, BS, Research Program Manager (9.00 calendar months requested for years 1-5) leads the Department of Pediatrics Program Management Team (PMT) and will support Dr. Traube by providing oversight for all operations, serving as a conduit for communications, monitoring progress toward scientific milestones, overseeing program and administrative staff (see below), liaising with the Research Business Office (RBO), coordinating meetings, and supervising intellectual property and regulatory compliance. Ms. Weinbaum has over 10 years' experience managing multiple P01 Program Projects, U01 Clinical studies, and Foundation awards with budgets of >\$15M per year. She will collaborate and serve as a conduit for communications to the NIH and lead site, between project team sites, the Data Coordinating Center (DCC), The Resource Data Center (RDC), and within the CPCCRN Network.

Keisha Small, MPH Regulatory Research Coordinator (9.00 calendar months in year 1; 6.00 calendar months requested per year 2-5) is a seasoned and effective research coordinator for the Department of Pediatrics from the Joint Clinical Trials office at Weill Cornell Medicine. She will assist the Project Manager with all regulatory paperwork and provide overall support of regulatory compliance and reporting, safety, and ethics reviews, as well as coordination with the CTSC as needed.

Isabel Leon, BS, Grants Portfolio Manager, RBO (2.40 calendar months requested per year) will meet with Dr. Traube and the designated Project Manager bimonthly to complete the day-to-day financial activities of the project. Responsibilities include monthly account management, administration of capitation fees, subcontractor invoice processing, subcontract initiations and amendments, financial compliance, and the de-obligation and reprogramming of funds as needed. A key component of her responsibilities will be ongoing financial review of transactions and examination of source documentation to assess the allowability of charges being billed to the grant. This practice ensures that only allowable and allocable charges are paid in accordance with uniform guidance.

Dakota Koop, BS, Administrative Assistant (3.00 calendar months requested per year), will assist Dr. Traube and the designated Project Manager in the coordination of tasks, including organization of all meetings,

collection and distribution of agendas, minutes, and task items, and coordination and reimbursement of required meetings and travel for the research team.

OTHER DIRECT COSTS

Central IRB Fees (\$111,616)

Total funds are requested (**\$111,616**) for IRB. In line with NIH requirements to maintain a single IRB structure for multi-center studies, we propose using an IRB that will be centralized through Utah and the DCC and the existing CPPCRN network. Utah IRB will invoice Weill Cornell Medicine quarterly and provide reporting and documentation for secondary review.

Planned IRB expenses for 14 clinical sites are as follows:

Year 1	Year 2	Year 3	Year 4	Year 5
\$ 41,856	\$ 17,440	\$ 17,440	\$ 17,440	\$ 17,440

Data Safety Monitoring Board (DSMB) Honorariums (\$22,500)

Total funds are requested (**\$4,500 per year**) for DSMB honorariums. We will recruit a data safety monitoring board to meet at least 3 times per year. The first meeting (early year 1) will be to get oriented to the study and give input into the study design before we commence the study itself. They will then meet 2-3 times/year to review interim analyses and a final time to review the final results. We will recruit five people to be on this board and provide each with a \$300 stipend for each 1-hour meeting.

Note: We have been advised by NIH in prior applications to defer selecting members of our DSMB until a project is finalized and funded. DSMB members are often leaders in the field, which then reduces the number of reviewers available to the NIH for the proposal. When funded, we will identify five members for the DSMB with the following expertise: participation in prior data-safety monitoring boards, expertise in pediatrics, critical care, clinical studies, and biostatistics.

Publications (\$3,000 YR. 3, \$6,000 YR. 4 and \$27,00 Yr. 5)

The HEAL Public Access Data Sharing Plan requires immediate dissemination of results. Total funds are requested in years three through five to cover the cost of publication and dissemination of this project's findings so that the broader scientific community benefit from the study's findings. These funds are primarily to be used to cover open access fees and printing of posters for conference presentations and dissemination.

Data Management Sharing Costs

WCM offers free data retention through its Institutional Data Repository for Research (WIDRR), a tool that was developed to help WCM researchers archive their datasets to be compliant with the Cornell University Data Retention Policy. Researchers can archive their dataset either in an approved public repository or in WIDRR. In any case, researchers will need to report the location of their datasets in WIDRR. We do not anticipate that there will be any cost to the PIs relating to data management/sharing for the proposed U01 studies.

Please see "Data Management & Sharing Plan" for further details and descriptions of these repositories.

Software Licensing (\$10,000)

Software licensing for HEAL capture access is requested for **\$2,000** per year.

Meeting Costs (\$13,500)

In Year 1, meeting costs for in-person 2-day meeting are requested to include room rental, IT/AV costs, catering, and printing needs. All investigators, DCC and program staff will meet to review protocols, timelines/milestones, data management and policies. **\$6,000 is requested for that purpose.**

In addition, MPIs and rotating key personnel will meet at conferences they are attending for in-person discussion of the project, its progress, and future steps. We envision a 90-minute in-person meeting of the entire team. The funding in these years will be used to reserve a room and AV equipment. **\$1,500 is requested for that purpose per years 1-5.**

CONSULTANT COSTS

Margaret Parker, MD, Medical Monitor, Consultant (\$10,000, all years, \$200 per hour for 50 hours per year) is an experienced pediatric critical care provider who was also the Director of the Pediatric Intensive Care Unit at Stony Brook University Hospital for 27 years. Dr. Parker has served on the Steering Committee of the Surviving Sepsis Campaign for the initial development and first revision of the guidelines, as well as on the Pediatric Surviving Sepsis Guideline Task Force. Dr. Parker will review study design prior to initiation of enrollment, review any serious adverse events, provide medical support to clinical sites and project team, and attend steering committee meetings as needed.

TRAVEL

Funds are requested (**\$225,000**) for travel for the Steering Committee (5), MPIs (3) team investigators and consultants (6) and project manager (2) to attend NIH HEAL Annual Investigators' Meeting and up to 2 (two) NIH HEAL KIDS Pain-sponsored meetings as well as present at additional conference(s). These funds will cover registration fees, hotel for 2 nights, airfare and transportation, and meals (\$2500 per person).

Funds are requested (**\$75,000 or \$15,000 per year**) for MPIs and rotating key investigators and staff (6) to travel to one national conference per year, with plans to meet in person in a small group annually while attending together.

Last, in **Year 1**, a larger travel and meeting budget (**\$37,500**) is for requested for required attendance of all key investigators for a first year planning meeting, including the DCC, to review preliminary data, timelines, milestones, IRB protocol and procedures, clinical site participation, data management sharing plans and HEAL Policies for data upload and dissemination. We have found in-person meetings to be much more effective than teleconferences or video conferences for the initial meeting.

CONSORTIUM/CONTRACTUAL

We will establish subaward agreements with Children's National Medical Center, The University of Utah, John Hopkins, and Ann & Robert H. Lurie Children's Hospital of Chicago; four domestic institutions, to support the efforts of Michael Bell, Richard Holubkov, Sapna Kudchadkar, and Erin Paquette.

1. Institution: Children's National Medical Center

Investigator: Bell, Michael (MPI)
Y1-\$196,866 Y2-\$199,326 Y3-\$201,860 Y4-\$204,472 Y5-\$206,716
Total, Y1-5: \$1,009,240

2. Institution: University of Utah

Investigator: Holubkov, Richard (MPI)
Y1-\$1,242,301 Y2-\$1,054,188 Y3-\$1,060,348 Y4-\$1,054,188 Y5-\$1,060,786
Total, Y1-5: \$5,471,811

3. Institution: John Hopkins

Investigator: Kudchadkar, Sapna (Co-I)
Y1-\$23,270 Y2-\$23,270 Y3-\$23,270 Y4-\$23,270 Y5-\$23,270
Total, Y1-5: \$116,350

4. Institution: Ann & Robert H. Lurie Children's Hospital of Chicago

Investigator: Paquette, Erin (Co-I)
Y1-\$41,424 Y2-\$20,711 Y3-\$20,711 Y4-\$20,711 Y5-\$20,711
Total, Y1-5: \$124,268

*See Subaward Budget and Budget Justification for more details

CLINICAL SITE AGREEMENTS

In addition to the four subcontracts listed above, the Research Business Office (RBO) will establish service contracts with up to **14 clinical subsites** to cover start-up costs (\$5,000 – year 1), annual pharmacy storage fees (\$2,500), and enrollment capitation fees (\$6,000 per subject).

These 14 participating clinical sites are listed below (See **Letters of Support**)

1	Arkansas Children's Hospital
2	Children's National Medical Center
3	Children's Hospital of Michigan
4	CHOC - Children's Hospital of Orange County
5	CHOP - Children's Hospital of Philadelphia
6	Christus Children's
7	MUSC - Medical University of South Carolina
8	Nationwide Children's Hospital
9	Texas Children' Hospital
10	University Hospitals Rainbow Babies & Children's
11	University of California, Davis Health
12	University of Pittsburgh
13	University of Utah Health
14	VCU - Virginia Commonwealth University

Fees for clinical sites are described below:

Startup Fee (\$5,000 per site in Year 1)

Total funds requested (**\$70,000**) to initiate clinical site subcontracts for enrollment.

Pharmacy Storage Fees (\$2500 per year per site)

Total funds requested for **\$175,000 (\$35,000 per year)** for pharmacy costs to included 2 study medications (Intravenous Acetaminophen and Ketorolac) and 2 fever reducing medications (Oral Acetaminophen and Ibuprofen).

Capitation Fees (\$6,000 per patient)

Total funds are requested for **\$3,864,000 (Y1: \$510,000; Y2: \$852,000; Y3: \$846,000; Y4: \$846,000; Y5: \$810,000)**. Funds are provided to support site PI and Research Coordinator effort to identify eligible patients and consent and Investigational Pharmacy costs to provide study medications. Clinical data collection (submitted to DCC) will include screening form for eligibility, detailed dosing of opioids and other sedative medications for the 5 days of the trial, collection of pain scores, delirium scores, and WAT scores that are obtained as part of normal patient care, a limited number of laboratory values, and a discharge form. Brief parent questionnaires will be provided as mandated by the Common Data Elements required by the HEAL initiative. Capitation fees will be invoiced quarterly.

FRINGE:

WCM's negotiated fringe benefit rate for federally funded grants is 32.5% of salaries and wages for faculty/staff and 25% of stipends for post-doctoral fellows.

INDIRECT COSTS:

WCM's federally negotiated indirect cost rate is 69.5% of modified total direct costs. This is inclusive of the first \$25,000 of each of the 14 clinical site agreements, to be established as consortium agreements.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	379,395.00
Section B, Other Personnel	1,102,678.00
Total Number Other Personnel	20
Total Salary, Wages and Fringe Benefits (A+B)	1,482,073.00
Section C, Equipment	0.00
Section D, Travel	337,500.00
1. Domestic	337,500.00
2. Foreign	0.00
Section E, Participant/Trainee Support Costs	0.00
1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other	0.00
6. Number of Participants/Trainees	0
Section F, Other Direct Costs	11,074,285.00
1. Materials and Supplies	0.00
2. Publication Costs	36,000.00
3. Consultant Services	50,000.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	6,721,669.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other 1	4,266,616.00
9. Other 2	0.00
10. Other 3	0.00
11. Other 4	0.00
12. Other 5	0.00
13. Other 6	0.00
14. Other 7	0.00
15. Other 8	0.00
16. Other 9	0.00
17. Other 10	0.00
Section G, Direct Costs (A thru F)	12,893,858.00
Section H, Indirect Costs	1,746,674.00

Section I, Total Direct and Indirect Costs (G + H)	14,640,532.00
Section J, Fee	0.00
Section K, Total Costs and Fee (I + J)	14,640,532.00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** University of Utah

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

A. Senior/Key Person												
	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Richard		Holubkov		PD/PI	212,100.00	1.2			21,210.00	7,424.00	28,634.00
2.	Ron	W	Reeder		Co-Investigator	169,335.00	1.8			25,400.00	9,906.00	35,306.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person	63,940.00	

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Administrative Assistant	1.8			8,735.00	3,581.00	12,316.00
1	QMS	1.2			12,723.00	5,471.00	18,194.00
3	Project Manager	24			205,148.00	89,484.00	294,632.00
1	Clinical Data Manager	9			88,385.00	28,283.00	116,668.00
1	Biostatistician	7.2			67,865.00	31,218.00	99,083.00
1	Director	1.8			27,241.00	10,352.00	37,593.00
8	Total Number Other Personnel					Total Other Personnel	578,486.00
Total Salary, Wages and Fringe Benefits (A+B)							642,426.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium

Organization: University of Utah

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

C. Equipment Description	
List items and dollar amount for each item exceeding \$5,000	
Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	<hr/>
	Total Equipment
Additional Equipment: File Name:	

D. Travel		Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)		37,500.00
2. Foreign Travel Costs		<hr/>
Total Travel Cost		37,500.00

E. Participant/Trainee Support Costs		Funds Requested (\$)*
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees		Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium

Organization: University of Utah

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	
2. Publication Costs	0.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	126,763.00
Total Other Direct Costs	126,763.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	806,689.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		54	806,689.00	435,612.00
Cognizant Federal Agency				435,612.00
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	1,242,301.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	1,242,301.00

L. Budget Justification*	File Name: BudgetJustification.Utah.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** University of Utah**Start Date*:** 07-01-2025**End Date*:** 06-30-2026**Budget Period:** 2**A. Senior/Key Person**

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Richard		Holubkov		PD/PI	212,100.00	1.2			21,210.00	7,424.00	28,634.00
2.	Ron	W	Reeder		Co-Investigator	169,335.00	1.8			25,400.00	9,906.00	35,306.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	63,940.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Administrative Assistant	1.8			8,735.00	3,581.00	12,316.00
1	QMS	0.6			6,362.00	2,736.00	9,098.00
3	Project Manager	19.2			165,054.00	74,719.00	239,773.00
1	Clinical Data Manager	6			58,923.00	18,855.00	77,778.00
1	Biostatistician	7.2			67,865.00	31,218.00	99,083.00
1	Director	1.8			27,241.00	10,352.00	37,593.00
8	Total Number Other Personnel				Total Other Personnel	475,641.00	
					Total Salary, Wages and Fringe Benefits (A+B)	539,581.00	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium

Organization: University of Utah

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	<hr/>
Additional Equipment: File Name:	Total Equipment <hr/>

D. Travel

Funds Requested (\$)*
37,500.00
<hr/>
Total Travel Cost 37,500.00

E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees	Total Participant Trainee Support Costs
<hr/>	<hr/>

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium

Organization: University of Utah

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	
2. Publication Costs	0.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	107,457.00
Total Other Direct Costs	107,457.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	684,538.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		54	684,538.00	369,650.00
Cognizant Federal Agency				369,650.00
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	1,054,188.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	1,054,188.00

L. Budget Justification*	File Name: BudgetJustification.Utah.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** University of Utah**Start Date*:** 07-01-2026**End Date*:** 06-30-2027**Budget Period:** 3**A. Senior/Key Person**

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Richard		Holubkov		PD/PI	212,100.00	1.2			21,210.00	7,424.00	28,634.00
2.	Ron	W	Reeder		Co-Investigator	169,335.00	1.8			25,400.00	9,906.00	35,306.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	63,940.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Administrative Assistant	1.8			8,735.00	3,581.00	12,316.00
1	QMS	0.6			6,362.00	2,736.00	9,098.00
3	Project Manager	19.2			165,054.00	74,719.00	239,773.00
1	Clinical Data Manager	6			58,923.00	18,855.00	77,778.00
1	Biostatistician	7.2			67,865.00	31,218.00	99,083.00
1	Director	1.8			27,241.00	10,352.00	37,593.00
8	Total Number Other Personnel				Total Other Personnel	475,641.00	
					Total Salary, Wages and Fringe Benefits (A+B)	539,581.00	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium

Organization: University of Utah

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	<hr/>
Additional Equipment: File Name:	Total Equipment <hr/>

D. Travel

	Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	37,500.00
2. Foreign Travel Costs	<hr/>
Total Travel Cost	37,500.00

E. Participant/Trainee Support Costs

	Funds Requested (\$)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	<hr/>
Number of Participants/Trainees	Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium

Organization: University of Utah

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	
2. Publication Costs	0.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	111,457.00
Total Other Direct Costs	111,457.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	688,538.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	54	688,538.00	371,810.00
Cognizant Federal Agency				371,810.00
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	1,060,348.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	1,060,348.00

L. Budget Justification*	File Name: BudgetJustification.Utah.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** University of Utah**Start Date*:** 07-01-2027**End Date*:** 06-30-2028**Budget Period:** 4**A. Senior/Key Person**

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Richard		Holubkov		PD/PI	212,100.00	1.2			21,210.00	7,424.00	28,634.00
2.	Ron	W	Reeder		Co-Investigator	169,335.00	1.8			25,400.00	9,906.00	35,306.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	63,940.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Administrative Assistant	1.8			8,735.00	3,581.00	12,316.00
1	QMS	0.6			6,362.00	2,736.00	9,098.00
3	Project Manager	19.2			165,054.00	74,719.00	239,773.00
1	Clinical Data Manager	6			58,923.00	18,855.00	77,778.00
1	Biostatistician	7.2			67,865.00	31,218.00	99,083.00
1	Director	1.8			27,241.00	10,352.00	37,593.00
8	Total Number Other Personnel				Total Other Personnel	475,641.00	
					Total Salary, Wages and Fringe Benefits (A+B)	539,581.00	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium

Organization: University of Utah

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

37,500.00

2. Foreign Travel Costs

Total Travel Cost **37,500.00****E. Participant/Trainee Support Costs**

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium

Organization: University of Utah

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	
2. Publication Costs	0.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	107,457.00
Total Other Direct Costs	107,457.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	684,538.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		54	684,538.00	369,650.00
Cognizant Federal Agency				369,650.00
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	1,054,188.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	1,054,188.00

L. Budget Justification*	File Name: BudgetJustification.Utah.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** University of Utah**Start Date*:** 07-01-2028**End Date*:** 06-30-2029**Budget Period:** 5**A. Senior/Key Person**

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Richard		Holubkov		PD/PI	212,100.00	1.2			21,210.00	7,424.00	28,634.00
2.	Ron	W	Reeder		Co-Investigator	169,335.00	1.8			25,400.00	9,906.00	35,306.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	63,940.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Administrative Assistant	1.8			8,735.00	3,581.00	12,316.00
1	QMS	0.6			6,362.00	2,736.00	9,098.00
3	Project Manager	18.6			159,756.00	73,023.00	232,779.00
1	Clinical Data Manager	6			58,923.00	18,855.00	77,778.00
1	Biostatistician	7.2			67,865.00	31,218.00	99,083.00
1	Director	1.8			27,241.00	10,352.00	37,593.00
8	Total Number Other Personnel				Total Other Personnel	468,647.00	
					Total Salary, Wages and Fringe Benefits (A+B)	532,587.00	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium

Organization: University of Utah

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	<hr/>
	Total Equipment

Additional Equipment: File Name:

D. Travel

	Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	37,500.00
2. Foreign Travel Costs	<hr/>
	Total Travel Cost

E. Participant/Trainee Support Costs

	Funds Requested (\$)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	<hr/>
Number of Participants/Trainees	Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

UEI*: LL8GLEVH6MG3

Budget Type*: Project Subaward/Consortium

Organization: University of Utah

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	
2. Publication Costs	12,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	106,735.00
	Total Other Direct Costs
	118,735.00

G. Direct Costs	Funds Requested (\$)*
	Total Direct Costs (A thru F)
	688,822.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	54	688,822.00	371,964.00
				Total Indirect Costs
				371,964.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
	Total Direct and Indirect Institutional Costs (G + H)
	1,060,786.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	1,060,786.00

L. Budget Justification*	File Name: BudgetJustification.Utah.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

UNIVERSITY OF UTAH

KEY PERSONNEL

Richard Holubkov, PhD Principal Investigator

Dr. Holubkov is a senior biostatistician for the Data Coordinating Center (DCC) and a Professor at the University of Utah. He has been the lead biostatistician for several large research networks and multicenter trials and has nearly four decades of experience in the design, management, analysis, and reported of data from prospective studies. These studies have included the DECAAF-II trial testing ablation treatments on subjects with atrial fibrillation, and the Artificial Valve Endocarditis Reduction Trial (AVERT) assessing thromboembolic events and other complications following heart valve replacement. In addition, Dr. Holubkov has been the senior biostatistician for the CPCCRN network since its inception in 2005. Dr. Holubkov will be responsible for all aspects of the proposed Data Coordinating Center (DCC) activities, including ensuring that appropriate data are collected to accomplish the goals of the study. Dr. Holubkov will participate in study investigator teleconferences and project meetings, oversee development of analysis datasets, as well as provide statistical expertise for the project. Dr. Holubkov will present interim analyses at DSMB meetings, oversee final analyses, and assist in abstract and manuscript preparation.

Salary and 35% benefits have been budgeted for 10% FTE (1.2 Cal Mos) for all years of the project period. Dr. Holubkov's base salary exceeds the current NIH salary cap; therefore, for purposes of this application, calendar months are calculated using the current cap of \$212,100.

Ron Reeder, PhD, Co-Investigator

Dr. Reeder is a Biostatistician and Associate Professor of Pediatrics at the University of Utah. Dr. Reeder has supported and directed two clinical research networks and has led several multi-center clinical trials and observational studies at the Utah DCC. Along with Dr. Holubkov, Dr. Reeder will be responsible for oversight of the proposed investigation at the Utah DCC. He will serve as the primary statistical contact, and he will direct the efforts of the Utah DCC to provide data management and statistical support for the proposed study.

Salary and 39% benefits have been budgeted for 15% FTE (1.2 Cal Mos) for all years of the project period.

OTHER PERSONNEL

Amy Goodman, PhD, Director

Dr. Goodman is a Director of Research & Science at the Utah DCC. She is a PhD in biomedical engineering with expertise in active implantable medical devices and neuromodulation for pain. Dr. Goodman has over 20 years of experience in clinical research leadership, both in early stage device companies (industry) and academic medical research (University of California, San Francisco, and University of Utah). She served the Director of the NIH-funded Phase III trial evaluating erythropoietin in newborns with HIE. Dr. Goodman will oversee all DCC activities and the DCC budget. She will establish and ensure consistent communication with the Principal Investigators. She will assure that the Utah DCC team is functioning efficiently to support the project. She will work closely with the Director of Regulatory Affairs and Quality Assurance to ensure regulatory requirements are addressed. She will ensure that team members are replaced and trained if there is a staff change at the DCC. She will also oversee the Project Manager and ensure the project milestones are being met.

Salary and 38% benefits have been budgeted for 15% FTE (1.8 Cal Mos) for all years of the project period.

Renee Kuhn, DCC Project Manager III

Ms. Kuhn has been a project manager at the DCC for over 12 years. Her previous experience includes managing the Therapeutic Hypothermia after Cardiac Arrest Trials (THAPCA Trials). Ms. Kuhn will be responsible for interfacing with the site personnel, managing the reliance and SIRB process, tracking regulatory documents, assisting with protocol and study document development, and working with the

Clinical Data Manager to assure high quality data submission. The Project Manager will develop the Manual of Operations, the protocol, and any training materials including online training as appropriate. She manages timelines, establishes and completes a risk assessment document, and creates a plan to mitigate risks identified. Ms. Kuhn will create the paper forms to be used for initial data collection prior to entry into the database. She will also be responsible for conducting remote monitoring activities as needed to verify data quality and provide site study training. Ms. Kuhn will coordinate research coordinator training and will conduct teleconference calls as needed. She will help to coordinate data harmonization, curation, and sharing efforts, and project management related to efforts at Utah. She will also serve as a point of contact for study teams and DCCs, and will facilitate registration of study information to the HEAL data ecosystem.

Salary and 49% benefits have been budgeted for 100% FTE (12.0 Cal Mos) for all years of the project period.

Jordan Bridges, DCC Project Manager III

Mr. Bridges has been with the DCC for four years and has a background in conducting randomized clinical trials. He currently serves as a project manager for the HEAL Effectiveness Research Network. Mr. Bridges will assist Ms. Kuhn with Project Management responsibilities for the OPTICOM study, including SIRB approval and remote monitoring.

Salary and 40% benefits have been budgeted for 75% FTE (9.0 Cal Mos) for year 1, and 50% FTE (6.0 Cal Mos) for years 2-5 of the project period.

Volker Freimann, Clinical Data Manager IV

Mr. Freimann has been with the DCC for nine years and has a background in conducting randomized clinical trials. He currently serves as a senior clinical data manager on multiple networks. Mr. Freimann will be responsible for identifying the data variables from the study protocol. He will also develop the database plan and create the electronic data capture system that sites will use to enter the data. He will be responsible for day-to-day monitoring of data submitted from the individual sites. He will prepare regular internal and external reports concerning data quality and will work closely with the Project Manager to determine areas of needed additional training at each site. He will also develop discrepancy rules that will automatically identify missing and errant data and will send nightly query notification to sites to initiate correction of data entry errors. The data manager will monitor query resolution status. He will also lock data prior to data safety monitoring board reviews, and will make any database changes, or update the database variables as necessary. He will lock the final dataset prior to study analyses.

Salary and 32% benefits have been budgeted for 75% FTE (9.0 Cal Mos) for year 1, and 50% FTE (6.0 Cal Mos) for years 2-5 of the project period.

Russell K. Banks, MS, Statistician III

Mr. Banks is a staff biostatistician at the Utah DCC. He has over eight years of experience providing statistical support for multicenter studies in pediatric critical care and emergency medicine. He earned a Masters of Science in Statistics degree from Utah State University in 2015.

Mr. Banks will be primarily responsible for data analysis. He will work with Drs. Holubkov and Reeder to conduct all statistical analyses. He will prepare formal data reports, and will provide all data safety monitoring board reports based on locked data at intervals during the trial. He will review all manuscript requests and create manuscript mapping plans for individual manuscripts as requested by the Principal Investigator. The manuscript plans will be coded during the enrollment period and iteratively reviewed by the lead authors. Data will be checked for missingness and accuracy. He will prepare final data analysis sets and will assist with final manuscript preparation. Mr. Banks will develop a public use data set or a final de-identified dataset for sharing with the funding agency.

Salary and 46% benefits have been budgeted for 60% FTE (7.2 Cal Mos) for all years of the project period.

Sally Perez, Sr., BS IT, Project Manager

Ms. Perez is a Sr. IT Project Manager for clinical projects at the Utah DCC. Ms. Perez received her Bachelor's Degree in Management Information Systems from Texas A&M University. She has over twenty years of project management experience and is a certified Project Management Professional (PMP). Ms. Perez supports numerous clinical projects in multiple networks and provides technical project management support from DCC startup through the enrollment phase. Sally is responsible for tracking and reporting the progress of projects and for highlighting risks in a continuing effort to protect the critical project timelines and milestones. Ms. Perez will ensure communication, timelines, and deliverables within the team. She will communicate with the DCC Project Manager any changes or issues that need to be discussed with the clinical team. She will attend regular team meeting to discuss needs, study progress, and development, and may attend key strategic meetings and calls.

Salary and 32% benefits have been budgeted for 25% FTE (3.0 Cal Mos) for year 1, 10% FTE (1.2 Cal Mos) for years 2-4, and 5% FTE (0.6 Cal Mos) for year 5 of the project period.

Maryse Brulotte, Director, Regulatory Affairs and Quality Assurance

Ms. Brulotte will assist the project manager with completion of the risk assessment and risk management plan for the OPTICOM study. Ms. Brulotte has assisted in the preparation of many risk management plans. She has regulatory experience and continuously updates the DCC's risk plans to reflect federal and international regulations. She will assure that risks are appropriately identified and mitigated at the beginning of the study. She will also help assure that the reports that are produced by the DCC study team reflect key risks and the study outcomes. She will provide consultation on any regulations that affect the study and will assist with any required IND reporting.

Salary and 43% benefits have been budgeted for 10% FTE (1.2 Cal Mos) for year 1, and 5% FTE (0.6 Cal Mos) for years 2-5 of the project period.

Tiffany Dubbelman, DCC Administrative Assistant

Ms. Dubbleman has provided administrative support for multiple projects at the Utah DCC for more than 5 years and will be responsible for setting up and organizing internal DCC meetings, setting up study-specific webinars that may be recorded, organizing trial documents at the DCC in our electronic storage system, and assuring that regulatory documents are stored and easily accessible. Ms. Dubbleman will also take minutes of meetings and will assist with setting up key study meetings with investigators, sites or others as requested. Ms. Dubbleman will also be responsible for assisting with organizing training materials on our electronic learning platform as needed.

Salary and 41% benefits have been budgeted for 15% FTE (1.8 Cal Mos) for all years of the project period.

Other Direct Costs

Travel (\$37,500/yr x 5 yrs = \$187,500)

Travel expenses are budgeted for 5 travelers to attend three HEAL Kids/Steering Committee meetings per year. (\$2,500/meeting x 3 meetings/year x 5 travelers/meeting)

Other Expenses

Computer (\$4,000/yr in yrs 1 & 3=\$8,000)

We budget \$2,000/laptop and required accessories. Two laptops/accessories are budgeted in year 1, and two laptops/accessories are budgeted in year 3.

Tableau

We budget \$5,000 years 1-5 to support the Tableau costs that are used for internal (to the network) and public facing reports.

Validated EDC

REDCap is a secure web-based application designed to manage study tools and surveys. The OPTICOM study will be developed in a REDCap environment that has been validated to meet the 21 CFR Part 11 regulations, thus ensuring our data meets high standards of integrity, reliability, and compliance with regulatory guidelines.

The individuals responsible for the validated system, technical aspects, and applications will formulate and execute compliance strategies and will ensure that new available features undergo appropriate validation prior to making them available within the validated system. They will also address any concerns related to data. Our staff, encompassing clinical data managers, project managers, IT security professionals, and system administrators, have undergone comprehensive training to enable them to use the validated system proficiently, ranging from data entry and management to reporting. Their training specifically focused on fulfilling the unique demands of a 21 CFR Part 11-compliant system.

The associated costs (\$5,000/year for all years of the project period) will cover the necessary hardware, including computing and storage capacities. These elements are crucial for the secure and smooth operation of the system.

IND contracting services

IND services will be contracted to IND specialists at the University of Utah at a rate of \$90/hour. 40 hours are estimated in year 1 of the project period, and 20 hours/year are estimated in each of years 2-5 of the project period.

Translations

Informed Consent Form translations are budgeted at \$250/site for the initial translation and \$75/site for each amendment. The initial translation is budgeted in year 1 of the project period. One amendment is budgeted per year in all years of the project period (including year 1).

eRoom Licenses

Annual eRoom licenses are budgeted for 2 licenses per engaged site. (\$59 x 2 individuals/site x 14 sites)

Onsite Monitoring

Annual onsite monitoring visits (\$3,300/domestic visit) are planned for each of the 14 sites. (\$3,300 x 14 sites x 5 years)

Florence eBinder

Yearly renewal fee for the online regulatory storage platform for participating sites. (\$1,000/year x 5 years)

Publication Fees

The HEAL Public Access Data Sharing Plan requires immediate dissemination of results. Thus, we budget funds in year 5 to cover publication fees associated with immediate publication. (\$3,000 x 4 manuscripts)

IT Recharge

An essential component of this application is a large Information Technology infrastructure, necessary to supporting all research projects who utilize the Utah Data Coordinating Center (DCC) staff, faculty, and services. The DCC IT Recharge Center provides the following services to all research projects and collaborators who require DCC services as part of their research:

- Help-Desk Support
- Maintenance of DCC hardware and servers
- Maintenance of DCC programs and applications
- Programming Solutions
- Access to state-of-the-art Data Center

Rates based off the number of DCC Full-Time Equivalents (FTE) and have been established based off the annual DCC IT personnel and non-personnel expenses necessary to maintain the IT infrastructure. We have

budgeted a total of \$238,158 over the project period. This was calculated using the Recharge Rate of \$14,437 per DCC Study FTE and \$1,855 per Admin FTE.

Indirect Costs

Indirect costs are calculated based on the Modified Total Direct Costs at the University of Utah's federally negotiated rate of 54%.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	319,700.00
Section B, Other Personnel	2,474,056.00
Total Number Other Personnel	40
Total Salary, Wages and Fringe Benefits (A+B)	2,793,756.00
Section C, Equipment	0.00
Section D, Travel	187,500.00
1. Domestic	187,500.00
2. Foreign	0.00
Section E, Participant/Trainee Support Costs	0.00
1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other	0.00
6. Number of Participants/Trainees	0
Section F, Other Direct Costs	571,869.00
1. Materials and Supplies	0.00
2. Publication Costs	12,000.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other 1	559,869.00
9. Other 2	0.00
10. Other 3	0.00
11. Other 4	0.00
12. Other 5	0.00
13. Other 6	0.00
14. Other 7	0.00
15. Other 8	0.00
16. Other 9	0.00
17. Other 10	0.00
Section G, Direct Costs (A thru F)	3,553,125.00
Section H, Indirect Costs	1,918,686.00

Section I, Total Direct and Indirect Costs (G + H)	5,471,811.00
Section J, Fee	0.00
Section K, Total Costs and Fee (I + J)	5,471,811.00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: XJ7MMPHBMGM

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Erin	D	Paquette		SubAward PI	212,100.00	1.2			21,210.00	5,515.00	26,725.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	26,725.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	
						Total Salary, Wages and Fringe Benefits (A+B)	26,725.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: XJ7MMPHBMGM7

Budget Type*: Project Subaward/Consortium

Organization: Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: XJ7MMPHBMGM7

Budget Type*: Project Subaward/Consortium

Organization: Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	26,725.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	55	26,725.00	14,699.00
Total Indirect Costs				14,699.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	41,424.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	41,424.00

L. Budget Justification*	File Name: Budget_Justification_Lur.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: XJ7MMPHBMGM

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Erin	D	Paquette		SubAward PI	212,100.00	0.6			10,605.00	2,757.00	13,362.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	13,362.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	
						Total Salary, Wages and Fringe Benefits (A+B)	13,362.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: XJ7MMPHBMGM7

Budget Type*: Project Subaward/Consortium

Organization: Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: XJ7MMPHBMGM7

Budget Type*: Project Subaward/Consortium

Organization: Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	13,362.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	55	13,362.00	7,349.00
Total Indirect Costs				7,349.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	20,711.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	20,711.00

L. Budget Justification*	File Name: Budget_Justification_Lur.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: XJ7MMPHBMGM

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

A. Senior/Key Person												
	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Erin	D	Paquette		SubAward PI	212,100.00	0.6			10,605.00	2,757.00	13,362.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		13,362.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates									
	Graduate Students									
	Undergraduate Students									
	Secretarial/Clerical									
0	Total Number Other Personnel							Total Other Personnel		
								Total Salary, Wages and Fringe Benefits (A+B)		13,362.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: XJ7MMPHBMGM7

Budget Type*: Project Subaward/Consortium

Organization: Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: XJ7MMPHBMGM7

Budget Type*: Project Subaward/Consortium

Organization: Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	13,362.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	55	13,362.00	7,349.00
Total Indirect Costs				7,349.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	20,711.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	20,711.00

L. Budget Justification*	File Name: Budget_Justification_Lur.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

UEI*: XJ7MMPHBMGM

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

A. Senior/Key Person												
	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Erin	D	Paquette		SubAward PI	212,100.00	0.6			10,605.00	2,757.00	13,362.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		13,362.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates									
	Graduate Students									
	Undergraduate Students									
	Secretarial/Clerical									
0	Total Number Other Personnel							Total Other Personnel		
								Total Salary, Wages and Fringe Benefits (A+B)		13,362.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

UEI*: XJ7MMPHBMGM7

Budget Type*: Project Subaward/Consortium

Organization: Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

UEI*: XJ7MMPHBMGM7

Budget Type*: Project Subaward/Consortium

Organization: Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	13,362.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	55	13,362.00	7,349.00
Total Indirect Costs				7,349.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	20,711.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	20,711.00

L. Budget Justification*	File Name: Budget_Justification_Lur.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

UEI*: XJ7MMPHBMGM

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

A. Senior/Key Person												
	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Erin	D	Paquette		SubAward PI	212,100.00	0.6			10,605.00	2,757.00	13,362.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		13,362.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates									
	Graduate Students									
	Undergraduate Students									
	Secretarial/Clerical									
0	Total Number Other Personnel							Total Other Personnel		
								Total Salary, Wages and Fringe Benefits (A+B)		13,362.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

UEI*: XJ7MMPHBMGM7

Budget Type*: Project Subaward/Consortium

Organization: Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

UEI*: XJ7MMPHBMGM7

Budget Type*: Project Subaward/Consortium

Organization: Ann & Robert H Lurie Childrens Hospital of Chicago

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	13,362.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	55	13,362.00	7,349.00
Total Indirect Costs				7,349.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	20,711.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	20,711.00

L. Budget Justification*	File Name: Budget_Justification_Lur.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RFA-HD-24-011

Ann and Robert H. Lurie Children's Hospital of Chicago

Budget Justification October 2023:

A. KEY PERSONNEL:

Dr. Erin Paquette (Co-investigator) (Site PI)- (1.2 CM in Y1 and 0.6 CM YR2-YR5)- is Associate Professor of Pediatrics at the Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine and Northwestern University Pritzker School of Law (by courtesy). She will spend 10% effort in year 1 and 5 % effort in year 2-5 in the research activities as outlined in this application. She will be responsible for all aspects of the project administration, direction and execution, including data analysis and dissemination of study findings.

Indirect Cost @ 55%

Covers all space, accounting, human resource, information services, legal and other generic services at Ann & Robert H. Lurie Children's Hospital of Chicago. It also covers maintenance and cleaning of offices, security, and the use of facilities at the hospital. Lurie Children's federally negotiated IDC is 55%.

Fringe Benefits The fringe benefit rate at Ann & Robert H. Lurie Children's Hospital of Chicago is 26%. This covers health insurance, taxes, unemployment insurance, life insurance, retirement plans and tuition reimbursement. The fringe benefits are directly proportional to that portion of personnel cost allocated for the project.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	80,173.00
Section B, Other Personnel	0.00
Total Number Other Personnel	0
Total Salary, Wages and Fringe Benefits (A+B)	80,173.00
Section C, Equipment	0.00
Section D, Travel	0.00
1. Domestic	0.00
2. Foreign	0.00
Section E, Participant/Trainee Support Costs	0.00
1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other	0.00
6. Number of Participants/Trainees	0
Section F, Other Direct Costs	0.00
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other 1	0.00
9. Other 2	0.00
10. Other 3	0.00
11. Other 4	0.00
12. Other 5	0.00
13. Other 6	0.00
14. Other 7	0.00
15. Other 8	0.00
16. Other 9	0.00
17. Other 10	0.00
Section G, Direct Costs (A thru F)	80,173.00
Section H, Indirect Costs	44,095.00

Section I, Total Direct and Indirect Costs (G + H)	124,268.00
Section J, Fee	0.00
Section K, Total Costs and Fee (I + J)	124,268.00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Johns Hopkins University

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Sapna		Kudchadkar		SubAward PI	212,100.00	0.6			10,605.00	3,606.00	14,211.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	14,211.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	
						Total Salary, Wages and Fringe Benefits (A+B)	14,211.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	14,211.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	63.75	14,211.00	9,059.00
Total Indirect Costs				9,059.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	23,270.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	23,270.00

L. Budget Justification*	File Name: BudgetJustification.JH.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Johns Hopkins University

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Sapna		Kudchadkar		SubAward PI	212,100.00	0.6			10,605.00	3,606.00	14,211.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	14,211.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	
						Total Salary, Wages and Fringe Benefits (A+B)	14,211.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 07-01-2025 End Date*: 06-30-2026 Budget Period: 2

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	14,211.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		63.75	14,211.00	9,059.00
Total Indirect Costs				9,059.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	23,270.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	23,270.00

L. Budget Justification*	File Name: BudgetJustification.JH.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Johns Hopkins University

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

A. Senior/Key Person												
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Sapna		Kudchadkar		SubAward PI	212,100.00	0.6			10,605.00	3,606.00	14,211.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		14,211.00

B. Other Personnel												
Number of Personnel*	Project Role*	Calendar Months				Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
		Post Doctoral Associates	Graduate Students	Undergraduate Students	Secretarial/Clerical							
0	Total Number Other Personnel									Total Other Personnel		
										Total Salary, Wages and Fringe Benefits (A+B)		14,211.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 07-01-2026 End Date*: 06-30-2027 Budget Period: 3

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	14,211.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		63.75	14,211.00	9,059.00
Total Indirect Costs				9,059.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	23,270.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	23,270.00

L. Budget Justification*	File Name: BudgetJustification.JH.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Johns Hopkins University

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

A. Senior/Key Person												
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Sapna		Kudchadkar		SubAward PI	212,100.00	0.6			10,605.00	3,606.00	14,211.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		14,211.00

B. Other Personnel												
Number of Personnel*	Project Role*	Calendar Months				Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
		Post Doctoral Associates	Graduate Students	Undergraduate Students	Secretarial/Clerical							
0	Total Number Other Personnel									Total Other Personnel		
										Total Salary, Wages and Fringe Benefits (A+B)		14,211.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	14,211.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	63.75	14,211.00	9,059.00
Total Indirect Costs				9,059.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	23,270.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	23,270.00

L. Budget Justification*	File Name: BudgetJustification.JH.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Johns Hopkins University

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Sapna		Kudchadkar		SubAward PI	212,100.00	0.6			10,605.00	3,606.00	14,211.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	14,211.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	
						Total Salary, Wages and Fringe Benefits (A+B)	14,211.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

UEI*: FTMTDMBR29C7

Budget Type*: Project Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 07-01-2028 End Date*: 06-30-2029 Budget Period: 5

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	14,211.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		63.75	14,211.00	9,059.00
Total Indirect Costs				9,059.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	23,270.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	23,270.00

L. Budget Justification*	File Name: BudgetJustification.JH.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

BUDGET JUSTIFICATION

DIRECT COSTS

SENIOR/KEY PERSONNEL

Dr. Sapna Kudchadkar, Co-Investigator, 5% effort/0.6 CM will participate in the study design and implementation as well as review of data analysis and interpretation of the results. As a pediatric anesthesiologist and intensivist with dedicated expertise in analgosedation in critically ill children, Dr. Kudchadkar's input will be integral to the successful conduct of this study.

INDIRECT COSTS

Fringe benefits are calculated at the Johns Hopkins University's standard rate of 34% for Faculty and Staff and 22.70% for Postdoctoral Fellows. Fringe benefits are calculated at these rates for all years of the study. F&A is calculated based on Modified Total Direct Costs (MTDC) at the Johns Hopkins University negotiated rate of 63.75% percent, effective May 10, 2023.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	71,055.00
Section B, Other Personnel	0.00
Total Number Other Personnel	0
Total Salary, Wages and Fringe Benefits (A+B)	71,055.00
Section C, Equipment	0.00
Section D, Travel	0.00
1. Domestic	0.00
2. Foreign	0.00
Section E, Participant/Trainee Support Costs	0.00
1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other	0.00
6. Number of Participants/Trainees	0
Section F, Other Direct Costs	0.00
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other 1	0.00
9. Other 2	0.00
10. Other 3	0.00
11. Other 4	0.00
12. Other 5	0.00
13. Other 6	0.00
14. Other 7	0.00
15. Other 8	0.00
16. Other 9	0.00
17. Other 10	0.00
Section G, Direct Costs (A thru F)	71,055.00
Section H, Indirect Costs	45,295.00

Section I, Total Direct and Indirect Costs (G + H)	116,350.00
Section J, Fee	0.00
Section K, Total Costs and Fee (I + J)	116,350.00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Children's Research Institute

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Michael	J.	Bell		PD/PI	212,100.00	2.4			42,420.00	8,060.00	50,480.00
2.	Vanessa		Madrigal		Co-Investigator	212,100.00	0.6			10,605.00	2,015.00	12,620.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	63,100.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Pharmacist	2.4			37,872.00	7,196.00	45,068.00
1	Total Number Other Personnel					Total Other Personnel	45,068.00
					Total Salary, Wages and Fringe Benefits (A+B)		108,168.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium

Organization: Children's Research Institute

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	_____
Additional Equipment: File Name:	Total Equipment _____

D. Travel

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Funds Requested (\$)*

Total Travel Cost _____**E. Participant/Trainee Support Costs**

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Funds Requested (\$)*

Number of Participants/Trainees**Total Participant Trainee Support Costs** _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium

Organization: Children's Research Institute

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 1

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	108,168.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	82	108,168.00	88,698.00
Total Indirect Costs				88,698.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	196,866.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	196,866.00

L. Budget Justification*	File Name: Budget Justification.CNMC.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Children's Research Institute

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Michael	J.	Bell		PD/PI	212,100.00	2.4			42,420.00	8,060.00	50,480.00
2.	Vanessa		Madrigal		Co-Investigator	212,100.00	0.6			10,605.00	2,015.00	12,620.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	63,100.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Pharmacist	2.4			39,008.00	7,412.00	46,420.00
1	Total Number Other Personnel					Total Other Personnel	46,420.00
					Total Salary, Wages and Fringe Benefits (A+B)		109,520.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium

Organization: Children's Research Institute

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium

Organization: Children's Research Institute

Start Date*: 07-01-2025

End Date*: 06-30-2026

Budget Period: 2

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	109,520.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	82	109,520.00	89,806.00
Total Indirect Costs				89,806.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	199,326.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	199,326.00

L. Budget Justification*	File Name: Budget Justification.CNMC.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Children's Research Institute

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Michael	J.	Bell		PD/PI	212,100.00	2.4			42,420.00	8,060.00	50,480.00
2.	Vanessa		Madrigal		Co-Investigator	212,100.00	0.6			10,605.00	2,015.00	12,620.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	63,100.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Pharmacist	2.4			40,178.00	7,634.00	47,812.00
1	Total Number Other Personnel					Total Other Personnel	47,812.00
					Total Salary, Wages and Fringe Benefits (A+B)		110,912.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium

Organization: Children's Research Institute

Start Date*: 07-01-2026

End Date*: 06-30-2027

Budget Period: 3

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	_____
Additional Equipment: File Name:	Total Equipment _____

D. Travel

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Funds Requested (\$)*

Total Travel Cost _____

E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Funds Requested (\$)*

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium

Organization: Children's Research Institute

Start Date*: 07-01-2026 End Date*: 06-30-2027 Budget Period: 3

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	110,912.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	82	110,912.00	90,948.00
Total Indirect Costs				90,948.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	201,860.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	201,860.00

L. Budget Justification*	File Name: Budget Justification.CNMC.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Children's Research Institute

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Michael	J.	Bell		PD/PI	212,100.00	2.4			42,420.00	8,060.00	50,480.00
2.	Vanessa		Madrigal		Co-Investigator	212,100.00	0.6			10,605.00	2,015.00	12,620.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	63,100.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Pharmacist	2.4			41,384.00	7,863.00	49,247.00
1	Total Number Other Personnel					Total Other Personnel	49,247.00
					Total Salary, Wages and Fringe Benefits (A+B)		112,347.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium

Organization: Children's Research Institute

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium

Organization: Children's Research Institute

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 4

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	112,347.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	82	112,347.00	92,125.00
Total Indirect Costs				92,125.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	204,472.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	204,472.00

L. Budget Justification*	File Name: Budget Justification.CNMC.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Children's Research Institute

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Michael	J.	Bell		PD/PI	212,100.00	2.4			42,420.00	8,060.00	50,480.00
2.	Vanessa		Madrigal		Co-Investigator	212,100.00	0.6			10,605.00	2,015.00	12,620.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	63,100.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Pharmacist	2.4			42,420.00	8,060.00	50,480.00
1	Total Number Other Personnel					Total Other Personnel	50,480.00
					Total Salary, Wages and Fringe Benefits (A+B)		113,580.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium

Organization: Children's Research Institute

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 5

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment _____

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost _____

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs _____

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

UEI*: M3KHEEYRM1S6

Budget Type*: Project Subaward/Consortium

Organization: Children's Research Institute

Start Date*: 07-01-2028 End Date*: 06-30-2029 Budget Period: 5

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	113,580.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	82	113,580.00	93,136.00
Total Indirect Costs				93,136.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	206,716.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	206,716.00

L. Budget Justification*	File Name: Budget Justification.CNMC.pdf
RESEARCH & RELATED Budget {F-K} (Funds Requested)	

BUDGET JUSTIFICATION

Children's National Hospital/Children's National Research Institute

A. KEY PERSONNEL

Michael J. Bell MD, MPI, (2.4 calendar months per year requested) is the Chief of Critical Care Medicine at Children's National Hospital and is the multi-PI for this application. Dr. Bell's qualifications are fully outlined in his bio-sketch. In brief, Dr. Bell has been NIH-funded for over 20 years and is an international expert in pediatric critical care medicine. He has been a member of CPCCRN – the network within which this study will be conducted – since 2004. His role in this proposal will be as a PI and coordinate activities related to the enrollment of subjects at CPCCRN sites and central pharmacy and (iv) the funding agency. He will work closely with the clinical and data coordinating centers to ensure the proper functioning of the study, will participate in the Executive Committee and Steering Committee meetings with the other 2 MPIs and will be responsible for the safe conduct of the study across the sites. Dr. Bell's base salary exceeds the current NIH salary cap; therefore, for purposes of this application, calendar months are calculated using the current cap of \$212,100.

Vanessa Madrigal MD, Co-Investigator (0.6 calendar months per year requested, Ethics Expert) is an Associate Professor of Pediatrics, an Attending Physician in the Pediatric Intensive Care Unit, and the Director of Ethics at Children's National Hospital. Dr. Madrigal has experience in participating in studies related to family communication and will serve on OPTICOM's Steering Committee for the duration of the trial. In this capacity, she will liaison with the CPCCRN Parent Network, the Diversity Expert and the Enrollment Expert to ensure that OPTICOM has as large an impact as possible within the global community of children with acute respiratory failure. She will participate in evaluating site enrollments to ensure that all provisions within the application are applied to maximize enrollment of subjects of all racial/ethnic and other characteristics are as represented as possible. Dr. Madrigal's base salary exceeds the current NIH salary cap: therefore, for purposes of this application, calendar months are calculated using the current cap of \$212,100.

B. OTHER PERSONNEL

Marissa Horrigan PharmD, Co-Investigator, Pharmacist (2.4 calendar months per year requested) is the Manager of Investigational Drug Services at Children's National. She has been involved in writing IND applications and manages multiple clinical trials at Children's National that are similar to the OPTICOM trial. For this application, Dr. Horrigan will be responsible for writing the Pharmacy Manual of Operations and train site Investigational Pharmacist teams on the conduct of OPTICOM. She will work with the DCC on implementation strategies for all sites to enroll subjects while maintaining blinding of subjects relative to the treatment groups of subjects.

Children's National Hospital/Children's National Research Institute will receive additional capitated funds for enrollment of subjects, startup, and pharmacy cost that are outlined in the University of Utah Budget and will be invoiced to Weill Cornell. (for additional details- see LOS)..

C. TRAVEL

Travel is budgeted and will be reimbursed through Weill Cornell Project Coordinator

D. EQUIPMENT

No equipment is requested for this project.

E. OTHER EXPENSES

No other expenses are anticipated.

Indirect Cost Rate for Children's National Hospital/Children's National Research Institute is 82%

Fringe Benefit Rate is 35%

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	315,500.00
Section B, Other Personnel	239,027.00
Total Number Other Personnel	5
Total Salary, Wages and Fringe Benefits (A+B)	554,527.00
Section C, Equipment	0.00
Section D, Travel	0.00
1. Domestic	0.00
2. Foreign	0.00
Section E, Participant/Trainee Support Costs	0.00
1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other	0.00
6. Number of Participants/Trainees	0
Section F, Other Direct Costs	0.00
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other 1	0.00
9. Other 2	0.00
10. Other 3	0.00
11. Other 4	0.00
12. Other 5	0.00
13. Other 6	0.00
14. Other 7	0.00
15. Other 8	0.00
16. Other 9	0.00
17. Other 10	0.00
Section G, Direct Costs (A thru F)	554,527.00
Section H, Indirect Costs	454,713.00

Section I, Total Direct and Indirect Costs (G + H)	1,009,240.00
Section J, Fee	0.00
Section K, Total Costs and Fee (I + J)	1,009,240.00

Total Direct Costs less Consortium F&A

NIH policy (NOT-OD-05-004) allows applicants to exclude consortium/contractual F&A costs when determining if an application falls at or beneath any applicable direct cost limit. When a direct cost limit is specified in an FOA, the following table can be used to determine if your application falls within that limit.

Categories	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Total Direct Costs less Consortium F&A	2,046,826	2,096,420	2,098,812	2,099,247	2,089,764	10,431,069

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 01/31/2026

1. Vertebrate Animals Section

Are vertebrate animals euthanized? Yes No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

Yes No

If "No" to AVMA guidelines, describe method and provide scientific justification

.....

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

Yes No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount (\$) *Source(s)

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? Yes No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? Yes No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: Yes No

If the answer is "Yes" then please answer the following:

*Previously Reported: Yes No

6. Change of Investigator/Change of Institution Section

Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

OMB Number: 0925-0001

Expiration Date: 01/31/2026

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	Specific Aims.pdf
3. Research Strategy*	Research Strategy.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	
6. Select Agent Research	SelectAgents.pdf
7. Multiple PD/PI Leadership Plan	MultiPI_Leadership Plan.pdf
8. Consortium/Contractual Arrangements	Consortium_Arrangements.pdf
9. Letters of Support	LOS.pdf
10. Resource Sharing Plan(s)	Resource_Sharing_Plan.pdf
11. Other Plan(s)	Data Management Sharing Plan.pdf
12. Authentication of Key Biological and/or Chemical Resources	Authentication.pdf
Appendix	
13. Appendix	

SPECIFIC AIMS

More than 24,000 critically ill children in the United States require invasive mechanical ventilation (MV) for acute respiratory failure (ARF) each year - an intrusive, painful, yet necessary and lifesaving procedure. While a wealth of information exists about optimizing analgesia-based sedation in adults with ARF, there is a critical knowledge gap for children with ARF. In contemporary practice, **children with ARF who require MV are exposed to high-dose opioids yet still experience breakthrough pain.** Inadequate pain control and prolonged opioid exposure put children at risk for chronic pain, opioid tolerance, opioid withdrawal, delirium, and other adverse complications to long-term cognitive and psychological well-being. There is a critical need for innovative strategies using non-opioid analgesics to improve outcomes for these medically vulnerable and under studied patients.

Our long-term objectives are to develop comprehensive approaches to pain management in children with ARF to decrease pain, reduce opioid exposure and improve long term outcomes – ultimately integrating these findings into clinical guidelines. Previous work has demonstrated enhanced pain control and decreased opioid exposure with adjuvant use of intravenous acetaminophen (IV-A) and/or intravenous ketorolac (IV-K). These studies, conducted predominantly in children after surgical procedures, have not been systematically evaluated in children with ARF. In our multi-center observational study of pharmacokinetics of sedatives in children with ARF on MV [R01HD12345], we found that children (n=70) were universally exposed to an extremely large amount of opioids -- the equivalent of >150 standard doses of morphine in the first 5 days alone. Nevertheless, >90% of subjects **still** experienced breakthrough pain. In comparing subjects from a site where IV-A and IV-K are used as part of routine analgesic-based sedation to subjects from a site without such an approach, we observed a substantial decrease in pain scores (mean FLACC score 1.22 vs. 0.48) and breakthrough pain events (mean 10.2/subject vs. 2.8/subject, p<0.005). We believe the overwhelming opioid exposure in this population, and proof of concept for effectiveness of these non-opioid medications at reducing acute pain, compels us to conduct a randomized controlled trial (RCT) of these promising alternatives.

To begin to address our long-term objectives, we hypothesize that a protocolized strategy of administering non-opioid adjuvant therapies to children with ARF can decrease pain. Secondarily, we hypothesize this strategy will decrease opioid exposure, delirium, withdrawal, and duration of MV. We will conduct this adequately powered multi-center RCT within the NICHD-funded Collaborative Pediatric Critical Care Research Network (CPCCRN) – a geographically diverse network of pediatric intensive care units with > 4000 annual admissions of children with ARF and a state-of-the-art Data Coordinating Center. We have constructed a diverse study team -- with expertise in analgesic-based sedation, pediatric ARF, ethics, and health disparities – that has partnered with the CPCCRN Family Network Collaborative to ensure diverse perspectives are represented in study execution. As ARF disproportionately affects Hispanic and Black children, it will be essential to ensure compositional diversity, with enrollment of underrepresented populations to maximize generalizability of the findings. The infrastructure of CPCCRN and experience of our study team position us to implement an innovative and groundbreaking multi-center RCT, Optimizing Pain Treatment In Children On Mechanical ventilation – the OPTICOM Trial, to test the following aims in this vulnerable and under-studied population:

Aim 1: Determine whether IV-A and/or IV-K reduce acute pain in children with ARF on MV.

In a factorial design, 644 children who are receiving opioids will be randomized equally into 1 of 4 arms: IV-A + Placebo (AO), IV-K + Placebo (KO), IV-A + IV-K (AK) or Placebo + Placebo (OO). The FLACC pain score will be measured every 4 hours for the first 5 days of MV and acute pain events (FLACC ≥4) will be quantified. Effects of acetaminophen and ketorolac will be determined by comparing the number of acute pain events between treatment groups, according to the 2 x 2 factorial design.

Aim 2: Determine whether IV-A and/or IV-K decrease opioid exposure in children with ARF on MV.

Opioid administration for the first 5 days of MV will be quantified in MME (consistent with HEAL common data elements [CDEs]). Groups and methodology will be similar to Aim 1.

Aim 3: Determine whether IV-A and/or IV-K decrease opioid withdrawal, delirium or length of MV.

Opioid withdrawal rates (assessed with the Withdrawal Assessment Tool [WAT] every 4 hours), delirium rates (assessed with the Cornell Assessment of Pediatric Delirium [CAPD] every 12 hours) and length of MV (in hours) will be quantified. Groups and methodology will be similar to Aim 1.

This innovative, adequately powered, multi-center RCT will provide urgently needed, high-impact, and actionable evidence to decrease acute pain, reduce adverse effects of opioids, and improve outcomes in a critical and underserved area of pain research: children with ARF who require MV. The findings of the proposed study will inform clinical practice guidelines that will affect thousands of children each year and will further the HEAL KIDS mission to advance the treatment and prevention of acute pain.

A. SIGNIFICANCE

I. Pain in Children with Critical Illness

The dogma of recent past in the field of pediatrics is the principle that “***children neither respond to nor remember painful experiences to the same degree that adults do***” (1,2). As a result, children were often under-treated for acute pain. To challenge this belief, randomized trials were conducted in infants undergoing surgical procedures and demonstrated decreased stress response in children with administration of analgesia (3). Therefore, a consensus was reached to provide protocolized pain management for children after surgical procedures (4,5). However, expert panels have been unable to provide clear recommendations for pain management in children with non-surgical acute medical conditions due to a lack of evidence-based studies establishing best practices (4,6). This includes patients with a common, life-threatening condition – children with acute respiratory failure (ARF) who require invasive mechanical ventilation (MV) -- despite considerable evidence that MV is a painful experience (6–8). The *Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)* trial will develop substantial proof that a protocolized approach using non-opioid based medications to treat acute pain can improve the health and well-being of children with ARF.

II. Inequitable Pain Management in Children

Any study focused on acute pain is obligated to acknowledge the long and disturbing history of racism in pain assessment and management (9). Medical reports from the 1820’s describe studies “proving” that black skin is thicker than white skin, thus concluding that Black people were somehow impervious to pain (10). Although medicine has made considerable progress over the past 200 years, implicit bias exists today. Systematic reviews show that nonwhite patients are still more likely to be undertreated for pain (11,12). Sadly, children are not spared from this phenomenon (13–15). Exacerbating the problem, ongoing under-enrollment of minority race/ethnicity children in pediatric critical care research studies limits generalizability of findings in a population at high-risk for mismanagement of pain (16–18). Furthermore, it is notable that ARF disproportionately affects Hispanic and Black children (19). **It is a medical – and ethical – imperative to address the ongoing disparities in acute pain management in pediatric studies.** An evidence-based approach involves: (i) deliberate inclusion of diverse perspectives, expertise, and personnel in study design, (ii) explicit empathy training of providers, and (iii) education of study team to improve enrollment rates of nonwhite children. **Our application has developed a sophisticated research-based plan to enhance significance of study results for ALL critically ill children and their families** (16,20–22).

III. Children with ARF: Exposure to Opioids

Each year, approximately 24,000 children in the United States require invasive mechanical ventilation (MV) – requiring the insertion and continued presence of an endotracheal tube in the trachea – for ARF (23). MV is widely acknowledged to be a painful experience, with patients routinely reporting non-procedural pain with routine care and even at rest (7,8). Moreover, routine respiratory care procedures (such as suctioning and repositioning) are known to trigger the pain response. As such, determining best practices for treating pain in children affected by ARF is medically necessary to avoid the increased morbidity that is attributed to mismanaged acute pain (6,24–26). Accepted practice involves administration of opioids – often as continuous infusions and intermittent dosing that necessarily increase as exposure continues – for patient comfort based on provider-perceived pain and/or agitation (27). Because the median duration of MV is 6.5 d [IQR 4–12 d] (28), there is a cumulative opioid exposure of > 150,000 days in children’s lives in the US each year. In fact, **our preliminary data suggest that children with ARF are given the equivalent of 156 doses of morphine in the first 5 days of MV alone**. This high-dose opioid exposure leads to physiological dependence, risks of withdrawal and risks to neurological well-being.

IV. Opioid Use: Short- and Long-term Morbidity

Studies have shown that pediatric opioid therapy is associated with significant short- and long-term complications (29,30). In the short term, opioids can cause respiratory depression and hypotension, while also having secondary effects on the gastrointestinal system (nausea, emesis, constipation) that can prolong hospitalization (5,31–34). Opioids can also cause hyperalgesia, paradoxically worsening pain (35). Studies have shown a relationship between opioids and development of delirium in children (36), which itself has been associated with substantial pediatric morbidity (37). With longer-term use, children develop opioid tolerance that can lead to iatrogenic withdrawal symptoms with attempts at discontinuation (38,39). Child survivors of ARF requiring MV have demonstrated lower IQ scores and increase in anxiety and post-traumatic stress symptoms after discharge, which may be due to prolonged opioid and sedative exposure (23,40). Children exposed to opioids are more likely to display cognitive decline than their age- and diagnosis-matched counterparts (40–42). In infancy, morphine has been associated with evidence of brain injury, with a dose-response relationship (43,44). **Although**

the long-term effects of high-dose opioid exposure in childhood remain understudied – including whether this exposure is a risk for future substance use disorder – it is undeniable that strategies that can minimize exposure using non-opioid approaches could significantly improve the health of critically ill children.

V. Alternatives to Opioids in ARF

Since the painful procedures related to MV are medically essential for survival from ARF, alternative approaches to minimize opioid exposure have been considered. More than a decade ago, the Society of Critical Care Medicine (SCCM) published Clinical Practice Guidelines for the Management of Pain, Agitation and Delirium in Adult Patients in the ICU. Among the recommendations for pain control for adults requiring MV: using behavioral pain scales for pain monitoring, targeting medications to allow for pain relief without oversedation, consideration of opioid-alternatives, and routinely monitoring for delirium. This ‘analgosedation’ approach (Fig 1) has been widely adopted for adults with ARF requiring MV because randomized trials have demonstrated improvement in outcomes (decreases in opioid/sedative exposure, mortality, duration of MV, delirium, opioid withdrawal, and others) (45–47). However, as highlighted in recent pediatric guidelines, **none of these studies included children** (6). We hypothesize that supplementing opioids with the non-opioid analgesics acetaminophen and/or ketorolac will (i) reduce pain and (ii) decrease opioid exposure in this vulnerable population.

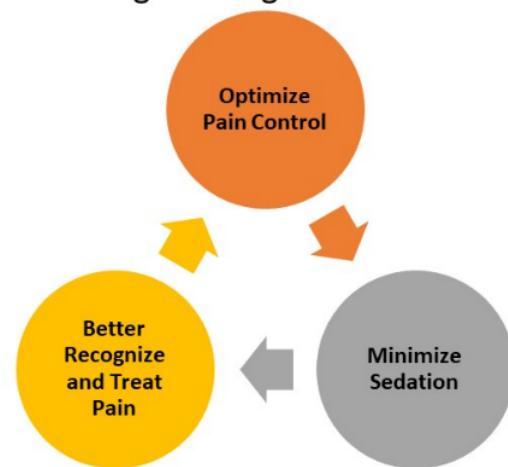
VI. Intravenous Acetaminophen (IV-A) and Ketorolac (IV-K)

Acetaminophen is one of the most widely used analgesics worldwide. Although debate exists regarding its exact mechanism of action, it acts centrally and independently of mechanisms related to opioid or non-steroidal anti-inflammatory medications (48). Oral acetaminophen has been used as an analgesic in pediatrics since 1955, but its wide variability in absorption and bioavailability are important considerations for critically ill children, limiting the utility of this administrative route (49). In 2010, the US Food and Drug Administration (FDA) labeled IV-A for use in children > 2 years of age, allowing predictable bioavailability for a variety of conditions. Safety and tolerability of IV-A in children < 2 years, including neonates, has been demonstrated in a number of studies (49–52). As for its effectiveness at pain management, a prospective cohort study in 106 children after scoliosis surgery showed that IV-A adjuvant therapy for post-operative pain resulted in decreased use of opioids ($p=0.002$) and shortened LOS ($p = 0.04$) (53,54). Similar results were found in an RCT of adults after cardiac surgery, where IV-A was also shown to reduce delirium (45).

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) that has been widely used as an analgesic since the 1990s, predominantly for post-operative pain (55). Its mechanism of action involves peripheral COX-mediated inhibition of prostaglandin synthesis (56). Relevant to our proposal, ketorolac improves pain control and decreases opioid exposure in adult patients after surgical procedures (57–59). FDA-labeled for patients over 17 years of age, its favorable side-effect profile and effectiveness also contribute to its common use in children of all ages, including infants (5,27,60–63). In an RCT involving 102 children after surgical procedures, more children achieved pain relief with ketorolac than with opiates alone (64) and it has become standard practice for many infants and children after cardiac surgery and other procedures (4,65). Similar to findings with IV-A, adding ketorolac to opioids in children after scoliosis surgery has been shown to improve pain control and reduce opioid exposure. In addition, it is cost-effective: adding ketorolac and/or acetaminophen to opioids has been shown to decrease hospital costs by hundreds of dollars for each patient (53).

In summary, the history of acute pain management in children has swung from the extreme of “no medications at all” to the contemporary practice of routine administration of high-dose opioids with significant side effects as well as negative long-term consequences. Acetaminophen and ketorolac – specifically in their intravenous forms (IV-A and IV-K) – are attractive adjuvants since they have demonstrated efficacy in reducing acute pain and minimizing opioid administration and side effects in a number of patient populations. Our preliminary data indicate that protocolized administration of IV-A and IV-K is likely to provide significant benefit to children with ARF. We are now poised to conduct an adequately powered multi-center RCT to provide powerful evidence to inform nationwide guidelines to optimize acute pain management in children with ARF.

Fig 1. Analgosedation



B. INNOVATION

The **OPTICOM** study is innovative in several important ways:

- **Approach:** This RCT challenges the current clinical practice paradigms for management and prevention of acute pain in critically ill children. It utilizes widely available medications (acetaminophen and ketorolac, both with a favorable safety profile and a long history of use) for a novel indication: analgesia associated with MV, and in a new population: infants and children. This “sensible science” represents a biologically plausible, logical, **simple and scalable approach** to a major public health problem. If acetaminophen and/or ketorolac improve pain control and decrease opioid exposure in children on MV, this study will generate actionable information that will lead to swift improvements in the critical care of children worldwide.
- **Experienced Network:** **OPTICOM** will be implemented by the premier Collaborative Pediatric Critical Care Research Network (CPCCRN) – **see LOS**. Funded by the National Institute of Child Health and Development (NICHD) since 2004, the network is made up of experienced core clinical sites, ancillary sites, and a centralized Data Coordinating Center (DCC). CPCCRN has completed more than 30 studies in critically ill children. CPCCRN has a long history of successful collaboration with a tried-and-true infrastructure for study execution, including centralized translation services, pharmacy and clinical monitoring, expertise in investigational new drugs (IND), data-sharing and analyses. The innovative, sophisticated, and long-standing infrastructure allows for efficient and effective operationalization of studies in the complex Pediatric Intensive Care Unit (PICU) environment.
- **Population:** Only a small fraction of the 1000+ funded HEAL projects involve children – and none focus on PICU patients, where children are exposed to the highest doses of opioids. Of the ~24,000 children with acute respiratory failure admitted to PICUs in the United States each year, more than 50% are under two years of age (28). These very young children are exposed to high-dose, near-continuous opioids for extended periods of time. There is significant concern in the scientific community regarding the effects of opioids on the developing brain, yet *this population has never been included in an adequately powered multi-center RCT designed to improve pain control and decrease opioid exposure*. **OPTICOM** will be the largest RCT exploring opioid-sparing agents in mechanically ventilated PICU infants and children. Furthermore, CPCCRN sites care for approximately 19% of children with acute respiratory failure in the entire US each year, and our selection of study sites from within CPCCRN was designed to identify an ethnically and geographically diverse sample of eligible patients. This will provide outstanding generalizability of our results to the larger pediatric critical care community.
- **Primary Outcome Measure:** Stakeholders (including parents of PICU patients, bedside nurses, and child survivors) have identified that **acute episodic pain is the single-most distressing aspect of ARF and MV**. Therefore, the primary outcome in this Acute Pain Clinical Trial (APCT) is the number of acute pain events. We will monitor pain, with a developmentally appropriate and validated measure, at multiple time points throughout this study.
- **Innovative Study Design:** This 2 x 2 factorial randomized controlled trial, with 4 treatment arms, will essentially deliver two separate RCTs with the cost and efficiency of one. A factorial design was chosen because it is the most efficient way to test the effect of two distinct treatments. This design will allow us to evaluate both acetaminophen and ketorolac for very little additional cost or complexity compared with testing only one drug. Additionally, this approach provides the ability to evaluate possible interactions between acetaminophen and ketorolac in exploratory analyses.
- **Enrollment of Under-Represented Populations:** We have intentionally designed the study to facilitate enrollment of patients generally under-represented in pediatric critical care research. We have consulted with our Family Network Collaborative (FNC) to include diverse perspectives in study planning and we have included investigators with expertise in bioethics and advocacy to reduce health disparities (**see LOS**). With their input, we will deliberately deploy a visibly diverse study team, as this has been shown to reduce medical mistrust and communication barriers associated with under-representation in clinical trials (66). Outreach efforts will involve ensuring our study materials are culturally and linguistically sensitive and accessible (67). Recruitment efforts, including the consenting process, will be done with respect and sensitivity, attention to the unique circumstances of each parent, and with transparency and humility (68).

We have involved all relevant stakeholders – including pediatricians, intensivists, nurses, pharmacologists, anesthesiologists, pain specialists, ethicists, and – most importantly -- former patients and their families – in our study design to further maximize study value, feasibility, and success. **This innovative, groundbreaking, large-scale, multi-site clinical trial is directly responsive to the Acute Pain Clinical**

Trials Program's overall goal to “establish or implement systematic and/or multimodal approaches for the diagnosis, assessment, and effective treatment of acute pain for pediatric patients”.

Our combined expertise leaves us poised to expand the field of HEAL-KIDS research to a medically vulnerable, under-studied, high-risk population: children with acute respiratory failure. This study has the potential to transform the care of children on invasive mechanical ventilation.

C. APPROACH

I. SUPPORTING DATA

a. Opioid Exposure in Children with ARF Requiring MV – Multicenter Study

The magnitude of opioid exposure in children with ARF is enormous. To illustrate this, we have examined the database for our multi-site NICHD-funded observational study investigating the pharmacokinetics of sedatives in children with ARF. In this population ($n = 70$), fully 100% of children were administered opioids as part of their routine care. A staggering quantity of opioids was administered, with a mean intravenous Morphine Milligram Equivalents (MME) of 15.6 MME/kg (± 10.6) over the first 5 days of MV. Assuming standard dosing of morphine at 0.05 - 0.1 mg/kg for children, **this finding represents >150 standard doses (30 to 60 per day)** for each child. Moreover, nearly 80% of these children developed delirium, and more than 40% developed symptoms of iatrogenic opioid withdrawal. In addition, we completed a retrospective analysis at one of our clinical sites and found that over a 12-year period, 15,281 children received opioids – with a median opioid exposure of 47.9 mg (IQR 12 – 173 MME) for children with ARF on MV.

b. Opioid Monotherapy for Acute Pain in Children with ARF

At this time, opioids are the single analgesic prescribed in most PICUs for children with ARF. In a national sample of 66,443 PICU patients, **ALL** of the 9,643 children on MV received opioids with a median duration of 41 (IQR 9-111) hours (27). In the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) trial of 2,449 intubated children, the study protocol for the intervention included only morphine and fentanyl as analgesics (28). In the 14 clinical sites in OPTICOM, current protocols for analgesic-based sedation include opioids as the sole analgesic without any protocolized approach to adjuvant therapies.

c. Pain Control is Inadequate Despite High-Dose Opioids

Despite the enormous opioid exposure, children with ARF still experience acute pain during their illness. In our multi-center study referenced above, 90% of children experienced one or more episodes of acute pain (defined as a FLACC score ≥ 4) during the first 5 days of MV. In the RESTORE trial, 16% of the children on the opioid-based sedation protocol experienced pain episodes **lasting >2 hours** at multiple points during the course of MV (28). It is clear that aggressive prescription of opioids is not enough; there is a need to optimize pain control in children with ARF.

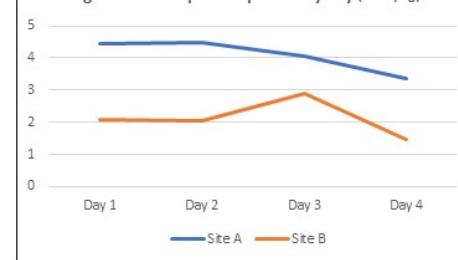
d. Data for IV-A and IV-K in Children with ARF

In our previous study of children with ARF on MV, we took advantage of structural issues at 2 sites to describe the effect of a protocolized approach to non-opioid based pain management. Specifically, Site A had an analgesic-based sedation approach that relied only on opioids for pain ($n=30$) while Site B routinely administered acetaminophen and/or ketorolac in addition to opioids ($n=15$). Despite identical enrollment criteria and similar patient characteristics (Table 1), median opioid exposure over the 5-day study period was greater in Site A compared to Site B (17.2 MME/kg vs. 13.6 MME/kg). At every measured time-point, opioid exposure was higher in the site that did not use acetaminophen and ketorolac (Site A) (Figure 2). Yet, children at Site B demonstrated substantially lower mean FLACC score (0.48 vs. 1.22), and an absolute 13% decrease in the incidence of acute pain (87% vs. 100%). Most notably, there were **significantly fewer pain episodes per patient** (mean 2.8 vs. 10.2, $p=0.0006$). In addition, withdrawal rates (47% vs. 70%) and percentage of days with delirium (44% vs. 57%) were substantially less in Site B.

Table 1. Comparison of patient demographics and outcomes with opioids alone (Site A) and with opioids + acetaminophen and ketorolac (Site B)

Patient Characteristics (mean, SD)	Site A (n=30)	Site B (n=15)	p-value
Age in years	3.64 (4.85)	3.25 (4.19)	0.80
FSS score on admission	6.50 (1.59)	6.44 (0.81)	0.89
Probability of Mortality	2.6% (3.0%)	2.5% (4.0%)	0.895
SaO ₂ /FiO ₂ ratio	184 (72)	216 (89)	0.47
Outcomes of Interest:			
Pain events per patient	10.2 (7.45)	2.8 (2.8)	<0.005
Average FLACC score	1.22 (2.13)	0.48 (1.59)	0.24
Opioid exposure (MME/kg)	18.9 (9.8)	14.2 (13.1)	0.18
Delirium rate	57%	44%	0.20
Opioid withdrawal rate	70%	47%	0.06

Fig 2. Median Opioid Exposure by day (MME/kg)



In a separate single-center pilot, we implemented a novel analgesic-first approach to sedation of children on MV where protocolized acetaminophen and ketorolac were added to standard opioid administration. The goal of this approach was to optimize pain management while decreasing opioid exposure, sedation, and potential side effects. Over a 3-month period, the PICU was able to demonstrate excellent pain control with less opioids, decreased use of benzodiazepines, reduced duration of delirium, and a shorter time to extubation when compared to similar patients who had been managed on an analgesic-based sedation protocol utilizing only opioids. However, no single pediatric ICU is sufficiently powered to study whether administration of these non-opioid adjuvant therapies to children with ARF can decrease pain; an adequately powered multi-center RCT is necessary to address this critical issue.

e. Addressing Implicit Bias in Pediatric Pain Management

A large body of literature shows that non-white patients are more likely to be undertreated for pain, as are other disparity health populations based on race, ethnicity, socioeconomic status, education level, and limited English proficiency (10–12,69–71). Children are not spared, as studies show that certain pediatric populations are less likely to receive peri-operative analgesia, more likely to experience suboptimal pain management for orthopedic injuries, and encounter disparities in anesthesia practices (72–74). Experts agree that there is a critical paucity of high-quality research on racial, ethnic, and socioeconomic disparities in pediatric pain management, specifically in the critical care space (72,75).

Implicit bias is defined as the unconscious stereotypes or attitudes that may affect our behaviors. For clinicians, this may result in differential assessments, decisions, and actions. This unconscious bias is unintentional but pervasive; it reflects the shortcuts born of automatic associations drawn from life experience, media, and other social influences. Paradoxically, implicit biases are often not congruent with a provider's stated beliefs and values, yet they have a significant impact on the quality of health care provided (13,14,69,76,77). Although these biases cannot be entirely eliminated, they can certainly be mitigated. Evidence shows that explicit education on implicit bias can decrease health care providers' prejudices, preconceptions, and stereotypes -- and subsequently improve patient treatment (21,22,78).

f. Lack of Compositional Diversity in Pediatric Critical Care Research

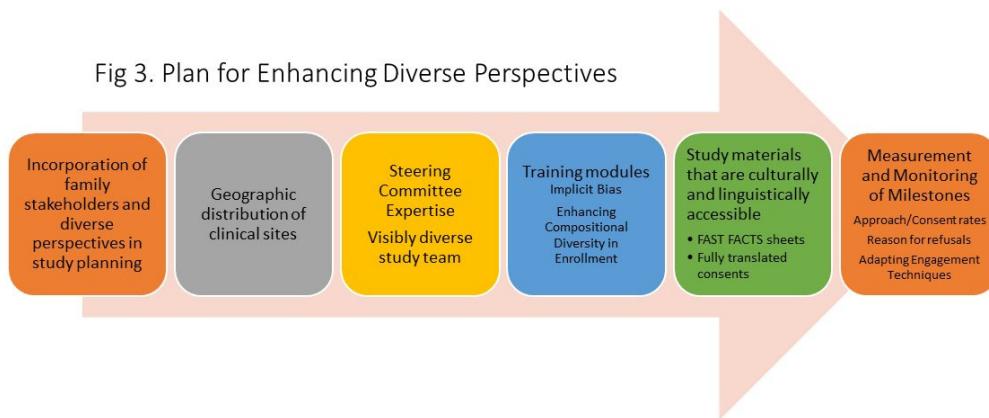
In order for clinical research to be generalizable, enrolled children need to accurately reflect the population affected by the disease under study. Research shows that disparity health populations are disproportionately affected by pediatric critical illness in general, and pediatric ARF in particular (79–84). Population-based studies have shown that "hot spots" for PICU admissions requiring MV reflect areas of higher social vulnerability and lower child opportunity (19,85,86). On a community-level, this vulnerability can be defined by 4 factors: education, employment, income, and housing quality (87). On an individual-level, social determinants of health (SDOH) reflect not just race and ethnicity, but also limited English proficiency, age, gender, housing instability, education level, unemployment, and food insecurity.

Unfortunately, the families with high individual- and community-level social risk are also the families least likely to enroll their children in research studies, especially critical care investigations (16,88,89). As such, we are unintentionally excluding the patients most likely to benefit from ARF research. Many barriers to enrollment have been identified and may be modifiable. With education of study staff, and deliberate changes in approach and consenting process, we will increase the compositional diversity in **OPTICOM** to ensure that the enrolled patients better reflect the pediatric population at highest-risk of disease (16,90,91).

g. Plan for Enhancing Diverse Perspectives (PEDP) To address implicit bias and enhance compositional diversity in this study, we have proposed a detailed Plan for Enhancing Diverse Perspectives (PEDP) (**see other plans for details**) (**Figure 3**). We

have incorporated a diverse team of stakeholders in the study planning process, including key personnel from historically underrepresented populations, multiple geographic locations, and at varying career levels. We are providing close mentoring for junior faculty members serving as site-PIs to facilitate the development of the next

Fig 3. Plan for Enhancing Diverse Perspectives



generation of clinical researchers in pediatric critical care. This is a multidisciplinary group, with prominent involvement of community-stakeholders (PICU parents and child survivors of ARF), physicians, nurses, clinical trialists, ethicists, and pain specialists. Our multi-step PEDP will provide education to study staff on implicit bias prior to study initiation and teach best-practices in approaching and enrolling a diverse population throughout the study. **Importantly, our selection of 14 clinical sites within CPCCRN was designed to allow for recruitment of a diverse population (see LOS).** We will monitor demographics of enrolled patients on a regular basis and provide corrective action if needed to enhance compositional diversity of enrollees. This equitable approach will enhance the scientific value of the study and allow for widely generalizable results. Finally, to ensure ongoing inclusion of diverse perspectives, regular team meetings will be held with rotating attendance by site-PIs, research coordinators, experts on ethics and diversity, and family representatives, as appropriate.

II. STRATEGY AND EXPERIMENTAL APPROACH

a. *Justification of study design: Need for blinding and randomization.*

In planning the **OPTICOM** trial, we initially considered a data analytics approach using a retrospective analysis of existing large data sets. However, the lack of a standardized approach to administration of non-opioid medications across PICUs would make it impossible to link the medication to the patient response. We also considered a prospective, observational cohort study that would allow sites to continue their normal practice of administering IV-A and IV-K and measure its effectiveness after controlling for covariates. Again, lack of consistency between sites and patients renders such an approach untenable --- and would still only lead to an association (as described in our pilot data) between non-opioid medications and effective pain relief.

A double-blind, randomized controlled trial is necessary to answer this vital question and advance the field. The randomization process minimizes bias and maximizes the rigor with which cause-and-effect relationships can be evaluated. Since the evaluation of the degree of pain for each patient is dependent upon nursing and physician assessments – and the FLACC score is our primary outcome – it is essential that clinicians are blinded to the treatment assignment for IV-A, IV-K or placebo. For the integrity of the hypothesis testing, it is also important that the study team at the sites is unaware of treatment assignment.

b. *Justification of primary outcome measure*

Inadequate analgesia is associated with a host of negative consequences, including immunosuppression, delirium, impaired sleep, and post-traumatic stress disorder (6). In fact, according to interviews with parents and PICU survivors, the single-most distressing aspect of MV was unrecognized or under-treated pain (24–26). It can be especially challenging to assess pain in children on MV as the children are all non-verbal, regardless of age, due to the presence of an endotracheal tube. This severely limits the use of self-report tools, such as the Wong-Baker Faces scale, Visual Analog Scale, Numeric Rating Scale, and Oucher Scale (6). Even in communicative patients, these self-report tools are unreliable in children under 6 years of age, who represent > 60% of patients with ARF. In 2022, the Society of Critical Care Medicine made a “strong recommendation” (the highest category available) to use the Faces, Legs, Activity, Cry, and Consolability (FLACC) scale in this population (6). The FLACC is an observational tool that quantifies pain behaviors, with 5 items scored 0-2, and total scores ranging from 0-10. A score of 4 or higher is the threshold widely used to designate significant pain (28,92). The FLACC has been validated in critically ill children, where it can be used across the spectrum of ages and developmental stages, with excellent reliability and validity (92,93). Higher FLACC scores have been independently associated with important clinical outcomes in intubated children, including upper airway obstruction and delirium (28,37,94). The FLACC is the most widely used tool (for both clinical care and research studies) to assess pain in intubated children in academic PICUs throughout the US (28,95). **From the perspective of parents, nurses, and physicians, decreasing episodes of acute pain is the most compelling and urgent need.** Therefore, our primary objective is to reduce the number of acute pain events in children with ARF on MV.

c. *Justification of Inclusion/Exclusion Criteria*

Inclusion criteria for the study are listed in **Table 2**. These have been deliberately designed to maximize patient eligibility, facilitating generalizability of findings to all children with ARF on MV, while still targeting the patient population who can most benefit from improved pain control. As outlined above, children with ARF who require an endotracheal tube (i.e., MV) frequently experience acute pain despite receiving an extraordinary amount of opioids. In contrast, children with ARF who do not need an endotracheal tube, either because of the presence of a tracheostomy or the use of non-invasive ventilation strategies, are dissimilar from our study group regarding pain and its management and will be excluded. We intend to enroll children as soon as possible after intubation to test our hypotheses in children who have not already had extensive opioid exposure before randomization.

As we intend to study children most in need of adjuvant therapies, we will limit enrollments to children who will be receiving opioids.

Table 2. Inclusion Criteria

Age ≤ 18 y
ARF requiring endotracheal intubation
Ability to approach family and obtain consent within 6 h of endotracheal intubation
Opioid infusion planned/started
Expected duration of IMV of > 48 h

Table 3. Exclusion Criteria

Tight temperature control required for clinical care
Contraindications to IV-A
Contraindications to IV-K
Requirement for prolonged neuromuscular blockade
Known pregnancy
Unwillingness of clinical team to allow randomization
Prior enrollment in the OPTICOM Trial

Exclusion criteria for the study are listed in **Table 3**. Several pediatric conditions, including but not limited to ischemic/traumatic brain injury, cardiac dysrhythmias, and others, require tight temperature control as part of routine care. Protocolized administration of antipyretics, such as acetaminophen and/or ibuprofen, are required for this standard practice, so it would not be ethical to provide placebo to these patients. In addition, we intend to exclude children with any of several FDA-recognized contraindications for IV-A (renal or liver dysfunction) and IV-K (known hypersensitivity, active/history of gastrointestinal bleeding, active/history of peptic ulcer disease, CNS bleeding, use of anticoagulants, renal dysfunction, thrombocytopenia and known drug interactions) from the study. Additionally, the primary outcome measure for this study will be the FLACC score (see justification above), which cannot be used in children on neuromuscular blockers. Diagnosed pregnancy will significantly alter the pain management of patients. Although all our clinical sites are committed to this study, we recognize that there will be instances where individual providers may feel that certain patients are inappropriate for enrollment/randomization. Finally, patients who have already been enrolled in the OPTICOM Trial will be excluded to maintain statistical integrity of the analysis.

d. Justification of Use of IV-A and IV-K as Study Medications

As we outlined in the Significance and Preliminary Data sections above, both IV-A and IV-K have demonstrated effectiveness in pain control in various patient populations and have excellent safety profiles in children. Because these two medications work via different mechanisms, we can evaluate both simultaneously (while exploring possible interactions; see statistical analysis plan), making efficient use of HEAL-KIDS funds. In addition, both medications are widely available and relatively inexpensive. If our hypothesis is substantiated, this will allow for broad implementation in PICUs across the United States, maximizing the scientific impact of this study.

e. Ethical Considerations: Inclusion of Children of All Ages

While infants and young children are disproportionately affected by ARF (>60% are <5 y old), they are often excluded from clinical trials. Although IV-A and IV-K are not labelled for very young children, there is frequent "off-label" use for other indications (for ex: ketorolac after congenital heart surgery in neonates; IV-acetaminophen for post-surgical pain in children <2 y old). Given the significant burden of acute pain and opioid exposure in these young patients, and the favorable risk/benefit relationship of IV-A and IV-K, we strongly believe that it would be unethical to exclude the patient population that is most likely to benefit from this study. We also note that the FDA has approved INDs for these medications for use in young children in other studies, and we have initiated the IND process for OPTICOM (49,60).

III. STUDY METHODOLOGY

a. Study Methods: As indicated within the Aims and justified in section IIa, a double-blinded, randomized controlled trial of IV-A and/or IV-K will be performed to test the aims proposed. Specifically, patients meeting inclusion/exclusion criteria will be approached for consent for enrollment in the study.

Immediately after consent, randomization will occur using a web-based system located at the **Data Coordinating Center (DCC)** at the University of Utah. Participants will be randomized via a web-based platform utilizing permuted-block randomization, stratified by site, in a 1:1:1:1 allocation across the 4 experimental groups in accordance with **Table 4**. The doses of IV-A and IV-K are the recommended maximum doses of the medications based on FDA recommendations. Medications will be staggered in such a manner that a medication is administered every 3 hours – active drug or placebo.

Table 4: Group Assignment and Dosing

Group	IV Acetaminophen Dose	IV Ketorolac Dose
AO	15 mg/kg* (maximum 600 mg) every 6 h	Placebo (IV 0.9% NSS) every 6 h
KO	Placebo (IV 0.9% NSS) every 6 h	0.5mg/kg (maximum 30 mg) every 6 h
AK	15 mg/kg* (maximum 600 mg) every 6 h	0.5mg/kg (maximum 30 mg) every 6 h
OO	Placebo (IV 0.9% NSS) every 6 h	Placebo (IV 0.9% NSS) every 6 h

*Note: For children <28 days old, IV-A dose will be 12.5 mg/kg every 6 hours, as per FDA recommendations.

b. Clinical Consideration: Stratification of Randomization by Study Site

The administration of sedation in children with ARF is thoroughly understudied – hence, there is no evidence to justify mandating a specific sedation regimen across sites. Instead, sites will employ their own sedation plans for children enrolled in this pragmatic trial. Study medications (IV-A and IV-K) will be strictly randomized as described above. All other clinical decisions will be made by the clinical team caring for the patient at the clinical site. Randomization will be stratified by clinical site to mitigate bias that may occur – ensuring that none of the 4 experimental groups is inadvertently overrepresented by any clinical site.

c. Clinical Consideration: Fever Management

A minority of children with ARF may develop fever during the 5-day study course. Clinicians may choose to treat fevers with oral formulations of acetaminophen or ibuprofen (delivered via nasogastric tube (NG) in children on MV). Children randomized to a study-arm that includes IV-A will already be receiving the maximum amount of acetaminophen daily. (Similarly, patients randomized to IV-K will be receiving the maximum amount of NSAIDs). However, blinding of practitioners as to study arms must be maintained for integrity of hypothesis testing. To allow for treatment of fevers with these oral medications without the risk of potential overdose, we will provide blinded medications to treat fever as needed. For patients randomized to experimental group AO, we will provide ibuprofen (10 mg/kg/dose via NG) and placebo (in place of acetaminophen). Similarly, for patients randomized to experimental group KO, we will provide acetaminophen (15 mg/kg/dose via NG) and placebo (in place of ibuprofen). Patients randomized to experimental group OO will receive both acetaminophen and ibuprofen, and patients randomized to AK will receive placebo only. This approach will be implemented after FDA review and approval of our IND application.

d. Data collection: Data regarding sociodemographics, medical diagnoses, medications and other information will be collected by study personnel. We plan to collect detailed dosing of opioids and other sedative medications for the 5 days of the trial, pain scores, delirium scores, opioid withdrawal scores, and laboratory values as detailed below. There will also be a limited number of parent questionnaires as mandated by the HEAL initiative (common data elements required for participation in HEAL; see below). The scope and specifics of the final dataset will be determined in consultation with the Steering Committee (including NIH and HEAL representation) for this U01 cooperative study.

e. HEAL-KIDS common data elements (CDE): We will rigorously collect all core CDEs (96). This will include the Physical Functioning measure (the PedsQL Inventory) and the Substance Use Screener (NIDA Modified Assist Tool-2) once, with parent providing a retrospective assessment of baseline functional values as soon as possible after enrollment. Similarly, we will collect the measures for Sleep (AWS+ Sleep Duration Items), Depression (PHQ-8), Anxiety (GAD-7), and Global Satisfaction with Treatment (PGIC) once, prior to discharge from the PICU. For CDEs that are appropriate (i.e.: Pain Interference and Pain Intensity), we will collect measures multiple times during this short window. Most importantly, we will have **multiple granular measurements of opioid exposure in morphine milligram equivalents (MMEs) as per the CDE definition**. This standardized approach will allow the HEAL-KIDS Research and Data Core (RDC) to harmonize the data from all the pediatric Acute Pain Clinical Trials and provide a large evidence-base for future studies. Importantly, we will include contact information in the consent, as we expect multiple ancillary studies leveraging this unique data set. With additional grant funding, future studies can assess post-discharge outcomes (for example: post-traumatic stress disorder, quality of life, and/or opioid dependence) in this cohort.

Aim 1: Determine whether IV-A and/or IV-K reduce acute pain in children with ARF on MV.

Stratifying by study site, 644 children who are receiving opioids will be randomized equally into 1 of 4 arms: IV-A + Placebo (AO), IV-K + Placebo (KO), IV-A + IV-K (AK) or Placebo + Placebo (OO). The FLACC pain score will be measured every 4 hours for the first 5 days of MV and acute pain events (FLACC ≥ 4) will be quantified. Effects of acetaminophen and ketorolac will be determined by comparing the number of acute pain events between treatment groups, according to the 2 x 2 factorial design.

Rationale: The validated FLACC score is the current criterion standard for the assessment of pain in mechanically ventilated children of all ages.

Study Methods: Site research personnel will be required to complete training and pass a certifying exam before activation of enrollment at the site. To ensure accuracy of assessments, the FLACC will be scored by trained PICU nurses. Upon enrollment of each patient, site research staff will provide 'just-in-time' FLACC refresher training to clinical personnel. As FLACC assessments are routinely done at all sites already, it is anticipated that this refresher will largely eliminate any variability in testing for this outcome.

Statistical Analysis Plan: The basis of the application is a 2 x 2 factorial RCT of IV-A and/or IV-K to reduce acute pain. A factorial design was chosen as the most efficient way to test the effect of two distinct treatments. The two primary analyses will be a comparison of those with versus without IV-A (AO/AK versus KO/OO) and a comparison of those with versus without IV-K (KO/AK versus AO/OO). This design will allow us to evaluate both IV-A and IV-K for very little additional cost or complexity compared with testing only one intervention. Additionally, this approach provides the ability to evaluate possible interaction between acetaminophen and ketorolac.

We will examine and report baseline characteristics of the population randomly assigned to the 4 treatments (AO, KO, AK, OO). Means, standard deviations, medians, and inter-quartile ranges will be used for continuous characteristics (e.g., age) while percentages will be used for categorical variables (e.g., sex).

Pain scores will be assessed every 4 hours from randomization until 5 days post-randomization (or extubation if the patient is extubated prior to 5 days). The primary study outcome, number of acute pain events (FLACC score ≥ 4), will be analyzed with a multivariable Poisson regression model. The two exposures are acetaminophen (IV-A vs placebo) and ketorolac (IV-K vs. placebo). Pediatric Risk of Mortality III (PRISM III), a measure of severity of illness, will be included as a covariate in the model to improve fit and increase precision of estimates. PRISM will be calculated with measurements within 2 hours prior to PICU admission through 4 hours after PICU admission or randomization, whichever comes first, to ensure treatment assignment cannot influence PRISM (98). We will estimate the relative number (rate ratio) of acute pain events with versus without acetaminophen as well as with versus without ketorolac. This ratio will additionally be scaled to the average duration of ventilation [up to 5 days] for interpretation. Incorporating both exposures (IV-A and IV-K, each vs placebo) into a single model provides more precise estimates of each drug's effect by controlling for the other. An offset term in the model will account for varying durations of mechanical ventilation, and a robust error estimator will account for over- or under-dispersion. While we expect approximate additivity of IV-A and IV-K effects (since the mechanisms of action are independent), we will initially fit a model including an IV-A/IV-K interaction term and evaluate its statistical significance. If not significant, we will report effects of each drug from a model without an interaction term; if there is (unexpected) significant interaction, our primary interest will be the effects of each treatment at each "level" of the other (i.e, reporting and contrasting outcomes in the 4 treatment strata). Since the power to detect a statistically significant interaction is limited, we will report outcomes in the 4 treatment groups in all instances.

In addition, we will conduct a comprehensive analysis to explore potential variations in treatment effects across key subgroups and across a range of individual risk profiles (97). Variations across key subgroups (e.g.: age, etiology of ARF) will be evaluated with an effect modeling strategy. The trial's statistical power may be constrained when it comes to detecting disparities in treatment effects among these subgroups. Therefore, we will complement our analysis by assessing the heterogeneity of treatment effects through a risk modeling approach. In this risk modeling approach, our initial step will involve developing a multivariable regression model to predict the number of acute pain events experienced by participants. This model will exclusively use pre-randomization covariates, without consideration of treatment assignment. This will provide an estimated "risk" score for each participant prior to their randomization into treatment groups. Subsequently, we will employ a second model to evaluate the impact of treatment across a continuous risk spectrum. This will be achieved by incorporating an interaction term that accounts for the treatment group and the estimated pre-randomization risk, allowing us to gauge treatment effects across a wide range of individual risk profiles.

Aim 2: Determine whether IV-A and/or IV-K decrease opioid exposure in children with ARF on MV.

Opioid administration for the first 5 days of MV will be quantified in MME (consistent with HEAL common data elements [CDEs]). Groups and methodology will be similar to Aim 1.

Rationale: While pain is the single most meaningful endpoint for stakeholders (child survivors and their parents), it is also important to reduce opioid exposure in these young, critically ill patients. Therefore, an overall reduction in opioid exposure is an important secondary objective for this study.

Study Methods: Cumulative opioid exposure will be measured from randomization until 5 days post-randomization or extubation. Granular data regarding administered opioids (including continuous infusions and bolus doses) will be collected for each child. Opioids of interest include (but are not limited to) morphine, fentanyl, remifentanil, hydromorphone, methadone, and oxycodone.

Statistical Analysis Plan: Cumulative opioid exposure will be calculated as per HEAL CDE standards, in MME/kg, and analyzed with a multivariable linear regression model. To reduce skewness of the distribution and to improve model fit, a log transformation, $\ln(x)$, will be applied to cumulative opioid exposure prior to modeling.

Analogously to Aim 1, the two exposures are acetaminophen and ketorolac. Strategy for evaluation of possible interaction will be analogous to Aim 1; if there is not significant interaction, we will estimate the relative amount of opioid exposure for participants with versus without acetaminophen and with versus without ketorolac. This will be reported as the ratio of geometric means.

Aim 3: Determine whether IV-A and/or IV-K decrease opioid withdrawal, delirium or length of MV.

Opioid withdrawal rates (assessed with the Withdrawal Assessment Tool [WAT] every 4 hours), delirium rates (assessed with the Cornell Assessment of Pediatric Delirium [CAPD] every 12 hours) and duration of MV (in hours) will be quantified. Groups and methodology will be similar to Aim 1.

Rationale: In addition to acute pain and opioid exposure, other important outcomes for children with ARF are (i) symptoms of physiological opioid withdrawal, (ii) development of delirium, and (iii) overall length of MV. Each of these outcomes may be mediated by pain. Decreasing delirium and withdrawal rates, and reducing length of MV, will improve outcomes in children with ARF.

Study Methods: Similar to the FLACC score, CAPD and WAT are routinely used at all clinical sites. Training and certification of site research personnel will be conducted prior to study initiation, as well as just-in-time refresher training of clinical site personnel upon patient enrollment.

Statistical Analysis Plan: Aim 3 outcomes include opioid withdrawal, delirium, and length of mechanical ventilation. Withdrawal will be assessed every 4 hours from initiation of opioid taper until discharge from the PICU. Delirium will be assessed twice daily from randomization until 5 days post-randomization or extubation. Length of mechanical ventilation (in hours) will be assessed from randomization until extubation.

Opioid withdrawal and delirium will be binary outcomes based on occurrence at any time. Each will be analyzed with separate multivariable Poisson regression models with robust error estimates. Analogous to Aim 1, the two exposures are acetaminophen and ketorolac. We will estimate the relative risks of opioid withdrawal and delirium with versus without acetaminophen and with versus without ketorolac.

Length of MV will be analyzed with a multivariable linear regression model. We will estimate the relative length of MV for participants with versus without acetaminophen and with versus without ketorolac. This will be reported as the ratio of geometric means. To reduce skewness of the distribution and to improve model fit, a log transformation, $\ln(x)$, will be applied to length of MV prior to modeling.

Intention to Treat: Primary analyses for all 3 aims will be conducted according to the intention to treat principle, e.g., all randomized participants will be included based on the treatment to which they were randomized. However, we recognize that oral formulations of acetaminophen or ibuprofen may be given for fever management. In an additional exploratory analysis, we will account for the potential effect of cumulative acetaminophen exposure (oral and intravenous formulations) during the study period in place of randomized to acetaminophen (yes, no).

SAMPLE SIZE AND POWER: Enrolling 644 total participants (161 in each of 4 arms) will provide **90% power** to detect the following outcomes:

- 1) Twenty-five percent reduction in average number of acute pain events (from 7 to 5.3, based on standard deviation of 6.1) during the intervention study period.

- 2) 21% relative reduction in cumulative opioid exposure (based on standard deviation of 0.84 for log-transformed cumulative opioid exposure);
- 3) 14% absolute reduction in opioid withdrawal (from 43% to 29%);
- 4) 13% absolute reduction in delirium (from 80% to 67%);
- 5) 18% relative reduction in duration of MV (based on a standard deviation of 0.72 for log-transformed duration of mechanical ventilation).

As we are testing two primary hypotheses, power calculations are based on a two-tailed t-test for independent samples with a conservative type I error rate (α) of 0.025.

IV. Potential Study Limitations

Children with ARF are notoriously difficult to assess. They are, by definition, nonverbal and often extremely young. Even though the FLACC score has been specifically validated in this population, it is possible that it may occasionally detect hyperactive delirium and/or agitation that is not pain-related. Even so, decreasing these episodes of discomfort is extremely important. In fact, parents, children, and PICU nurses have identified this as the single most crucial area for improvement in the care we provide to children on mechanical ventilation.

The pragmatic study design of OPTICOM (with protocolized administration of IV-A and IV-K, without otherwise dictating a specific sedation regimen) is a major strength, as it will increase trial feasibility and allow for greater generalizability of results. However, with 14 clinical sites participating, there will be some heterogeneity in sedation approach. To ensure balance between treatment groups within each site, randomization will be stratified by site. In addition, although we observed a 70% reduction in acute pain events with treatment in our two-center observational study, we are conscious that the treatment effect may be moderated in a large multicenter trial. Therefore, this study is powered to detect a reduction of only 25%.

Finally, in this Acute Pain Clinical Trial (APCT), we are not able to include post-discharge measurements of psychological health and family functioning as this would greatly increase trial cost and decrease feasibility of completing the research within the 5-year study period. However, with granular description of opioid exposures, the detailed data set generated by this study will be an invaluable resource for ancillary studies and future longitudinal investigations that assess the impact of acute pain and opioid exposure on young children's long-term health.

D. CLINICAL TRIAL MANAGEMENT

Program Organization. OPTICOM is designed to foster collaboration and communications, coordinate data management and sharing, and oversee fiscal and regulatory compliance efficiently (**Figure 4**). The OPTICOM leadership includes **Dr. Chani Traube (MPI, contact)**, Chair of the CPCCRN Steering Committee and a widely respected clinical researcher with expertise in pediatrics, pediatric critical illness, delirium, sedation, and PICU outcomes; **Dr. Michael Bell (MPI)**, an expert in leading large, multi-center, pediatric critical care trials; **Dr. Richard Holubkov (MPI)**, Director of DCC and senior biostatistician. Coinvestigators include **Dr. Sapna Kudchadkar**,

Vice Chair for Pediatric Anesthesiology and Critical Care Medicine at Johns Hopkins with expertise in pediatric pain management, **Dr. Joy Howell**, Vice Chair for Diversity in the Department of Pediatrics at Weill Cornell Medicine, and **Dr. Erin Paquette**, pediatric critical care clinician and ethicist at Northwestern Medicine. Dr. Traube will ensure that the overall scientific agenda is carried out and that resources are used effectively and efficiently with the support of a dedicated, experienced **Program Manager** who will provide oversight for all operations, serve as a conduit for communications, monitor progress toward scientific milestones, oversee program and administrative staff, and liaise with the **Research Business Office (RBO)**. They will coordinate with **Data Coordinating Center (DCC)** Director and **DCC Program Managers**. Under the management of MPI Dr. Holubkov, the DCC at the University of Utah (which has successfully coordinated >140 multi-center studies) will provide comprehensive clinical research support to include database development, single IRB services, expertise in investigational new drug (IND) submissions to the FDA, training of study staff at the 14 clinical sites, study initiation, clinical data management, sophisticated data validation, biostatistical expertise, and formal study closure procedures. In addition, the DCC will **coordinate with the HEAL-KIDS Pain Resource and Data Center (RDC)**.

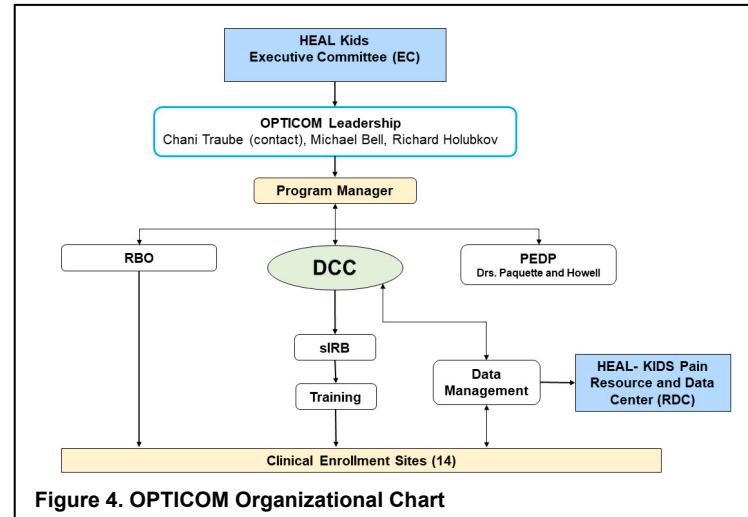


Figure 4. OPTICOM Organizational Chart

Resource and Data Center (RDC) for all data sharing, register studies with the HEAL Data Platform, and prepare Public-Use Datasets through established NIH data repositories. Since a vital part of our clinical trial management is monitoring of the objectives outlined in our **PEDP**, Dr. Traube and the DCC will monitor enrollment monthly to ensure we are meeting our targets for inclusion of patients historically underrepresented in research. Both the University of Utah and WCM also have well-established NIH-funded Clinical Translational Science Centers that have committed additional support as needed (**see LOS**).

In accordance with the cooperative agreement requirements, a Steering Committee (SC) will be assembled, and will consist of the 3 MPIs, NICHD HEAL-KIDS program representative, full-time Project Managers, Medical Monitor, and our Co-investigators. In year 1, the SC will meet for a 2-day meeting to review data elements, timeline, milestones, IRB protocol and procedures, data management sharing plans, and HEAL Policies for data upload and dissemination.

Collaboration with HEAL-KIDS Acute Pain Clinical Trials Program. MPIs and Key Personnel will also be members of the HEAL-KIDS Executive Committee, attend the meetings organized by the RDC, and collaborate scientifically with the other U01 awardees. This will include attending the annual NIH HEAL Investigators meeting and NIH-sponsored workshops, and other NIH HEAL KIDS sponsored meetings as needed.

Integration between DCC and Clinical Sites. The **OPTICOM** trial will be implemented by the CPCCRN network, comprised of core clinical sites, ancillary sites, and the centralized DCC. This fully integrated organizational infrastructure will allow for efficient operationalization of OPTICOM in the complex PICU environment. The already-established collaboration between the DCC and the 14 clinical sites will ensure the ability to achieve goals on-budget and on-time (**see Core Milestones below**).

Fiscal Accountability and Management. Fiscal accountability and transparency will be ensured by the RBO team, which offers targeted, end-to-end, research portfolio management, with up-to-the-minute expenditure reports and immediate funds transfer, ensuring proper spending and compliance. Tracking of expenditures relative to milestones will allow Dr. Traube and RBO to track productivity relative to spending. This will provide Dr. Traube with the ability to monitor scientific progress, rapidly intercede if difficulties occur, and, when appropriate, reallocate funds in consensus with the NICHD and Steering Committee.

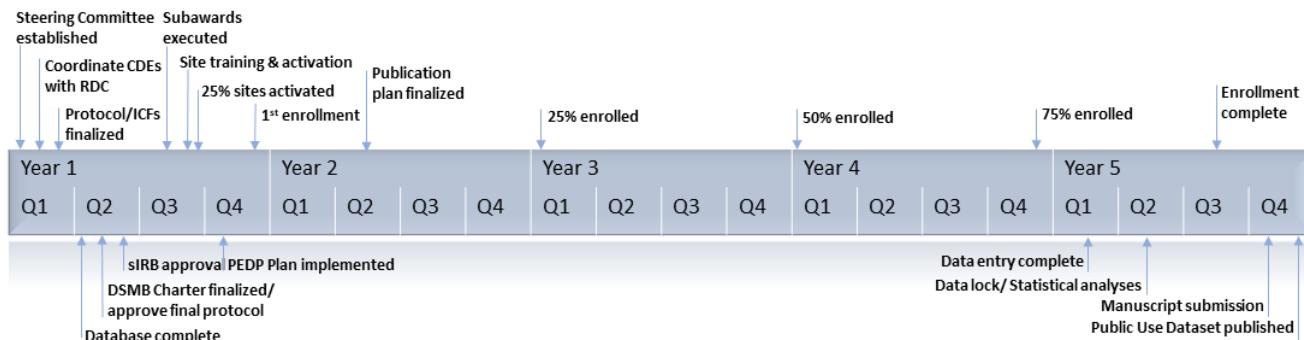
Risk Assessment and Management Plan. Consistent with the International Conference on Harmonization's Good Clinical Practices (98), OPTICOM has been designed to enhance human-subject protection and reliability of study results (**see Facilities DCC Fig 11** for details).

Patient risk and mitigation strategies. To enhance patient safety, we have established consistent processes for adverse event reporting and included Dr. **Margaret Parker**, with >27 years' experience as a PICU Director, who will consult as Medical Monitor (**see LOS**). The Medical Monitor will be unblinded to group assignment and work to ensure that any patient safety concerns are addressed immediately. We will also have a 5-member NICHD-appointed Data Safety Monitoring Board (DSMB) that includes expertise in pediatrics and critical care, clinical trials, and statistical analyses. A detailed DSMB report will be generated by the DCC for semi-annual meetings.

Study risk and mitigation strategies: A risk to the study is failure to enroll sufficient patients. As we expect >3000 patients to meet enrollment criteria at our 14 clinical sites during the study period, we believe our patient numbers support the feasibility of the trial. However, if under-enrollment occurs, we have 10 additional CPCCRN sites that could later be added to the study. A risk to the PEDP is that we will not be successful in enrolling children who have historically been under-represented in critical care research. To mitigate this risk, we will regularly assess approach rates, consent rates and reasons for refusal. We will consult with our Family Network Collaborative and be prepared to adapt our engagement techniques to improve compositional diversity.

E. CORE MILESTONES.

Core milestones are described in the figure below (details in PHS HS & CT 2.7)



PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 01/31/2026

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *

Yes No

Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.

Are Human Subjects Involved

Yes No

Is the Project Exempt from Federal regulations?

Yes No

Exemption Number

1 2 3 4 5 6 7 8

Other Requested Information

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)	Yes

Section 1 - Basic Information (Study 1)

1.1. Study Title *

Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)

1.2. Is this study exempt from Federal
Regulations *

Yes No

1.3. Exemption Number

1 2 3 4 5 6 7 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants? Yes No

1.4.b. Are the participants prospectively assigned to an intervention? Yes No

1.4.c. Is the study designed to evaluate the effect of the intervention on the participants? Yes No

1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome? Yes No

1.5. Provide the ClinicalTrials.gov Identifier (e.g.

NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- Acute Respiratory Failure(ARF)
- Analgesics, Opioid

2.2. Eligibility Criteria

Children 0-18 years old with acute respiratory failure requiring invasive mechanical ventilation

Inclusion Criteria

1. Age < 18 y
2. ARF requiring endotracheal intubation
3. Ability to approach family and obtain consent within 6 h of endotracheal intubation
4. Opioid infusion planned/started
5. Expected duration of IMV of > 48 h

Exclusion Criteria

1. Tight temperature control required for clinical care
2. Contraindications to intravenous acetaminophen
3. Contraindications to intravenous ketorolac
4. Requirement for prolonged neuromuscular blockade
5. Known pregnancy
6. Unwillingness of clinical team to allow randomization
7. Prior enrollment in the OPTICOM Trial

2.3. Age Limits	Min Age:	1 Days	Max Age:	18 Years
2.3.a. Inclusion of Individuals Across the Lifespan				Individuals_Across_Lifespan.pdf
2.4. Inclusion of Women and Minorities				Inclusion_Women_Minorities.pdf
2.5. Recruitment and Retention Plan				Recruitment_and_Retention_Plan.pdf
2.6. Recruitment Status				Not yet recruiting
2.7. Study Timeline				Study_Timeline.pdf
2.8. Enrollment of First Participant		06/01/2025		Anticipated

INCLUSION OF INDIVIDUALS ACROSS THE LIFESPAN - OPTICOM

In selecting participants for this study, due notice is taken of the NIH's policy concerning inclusion of participants across the lifespan in clinical research. **OPTICOM** is an interventional study designed for critically ill children with acute respiratory failure. While adults also suffer from acute respiratory failure, the clinical, pain, and medication-related characteristics are different in the pediatric and adult age groups; therefore, we plan to focus on children in this HEAL-KIDS Acute Pain Clinical Trial. We will enroll all children, 0-18 years old; we will not exclude any patients based upon age. (As more than 50% of children with acute respiratory failure are less than 2 years old, this age range was chosen to maximize our capacity to generalize study findings to the larger pediatric population at risk of the disease). Furthermore, the outcome measures used in the proposed study (FLACC pain scores, opioid exposure in MME/kg, withdrawal and delirium assessments, and parent-proxy questionnaires as defined in the HEAL-KIDS common data elements) have all been validated for use in children 0-18 years old.

INCLUSION OF WOMEN AND MINORITIES

In selecting participants in the proposed project, due notice is taken of the NIH Policy concerning inclusion of women and minorities in clinical research populations. No exclusions are or will be made on the basis of sex, race, or ethnicity.

Rationale for Selection

The proposed study will be open to children of all ethnic and racial backgrounds and gender identities, as all children are at risk for acute respiratory failure. We will not exclude people based on their race, ethnicity, gender, or sex, or any other background or identity-related characteristic.

Planned Distribution

Given the demographics of children with acute respiratory failure at our recruitment sites, and our prior history of enrollment, we expect the study sample will be 44% female. We expect 50% racial minority participants (35% Black/African-American, 7% Asian, 2% American Indian/Alaskan, <1% Native Hawaiian, 5% Other or Mixed race), and 21% Hispanic/Latinx.

Detailed Plans for Increasing Enrollment of Minority Participants

Our selection of study sites from within CPCCRN was designed to identify an ethnically and geographically diverse sample of eligible parents. We will recruit from 14 different sites to increase the possibility of a diverse sample. We anticipate minority accrual from the study sites will be successful due to our **comprehensive Plan to Enhance Diverse Perspectives (PEDP)**, which will address potential barriers to minority access and enrollment on clinical trials. The plan focuses on four main areas to increase minority access to care, including 1) education, 2) at the organizational level, 3) the clinical trials interface, and 4) outreach efforts.

- 1) All study team members will be provided with education on avoiding implicit bias and using communication strategies to reduce medical mistrust and demonstrate cultural humility.
- 2) We will employ a visibly diverse team of investigators and research coordinators, as this has been shown to reduce medical mistrust and communication barriers associated with BIPOC under-representation in clinical trials.
- 3) On the clinical trials interface, we will emphasize the intentional focus on improving care for BIPOC parents.
- 4) Outreach efforts will involve ensuring our study materials are culturally and linguistically sensitive and accessible. As for every participant: recruitment efforts, the consenting process, and intervention delivery will all be done with respect and sensitivity, attention to the unique circumstances of each parent, and with transparency and humility. We have partnered with CPCCRN's Family Network Collaborative and will have parents of prior PICU patients available to speak with the parents of potential OPTICOM study participants.

Plans for Taking Sex/Gender, Race, and Ethnicity into the Design and Analysis

There will be no exclusion based on sex/gender, race, or ethnicity. Identified sex, race, and ethnicity will be assessed and analyzed to determine their impact on results. The analysis of race/ethnicity differences will be facilitated by the expected diversity of our sample, and evaluation of outcomes will be unbiased. Our investigative team members have a track record of successfully recruiting diverse participants and will monitor study recruitment to minimize selection biases.

RECRUITMENT AND RETENTION PLAN

Recruitment:

This multisite, randomized controlled trial (RCT) will enroll 644 critically ill children with acute respiratory failure (ARF) who require invasive mechanical ventilation (MV). These children will be recruited from 14 Pediatric Intensive Care Units (PICU) within a 48-month recruitment period (Years 0.8 through 4.8). Sites will include:

1. Arkansas Children's Hospital
2. Children's National Medical Center
3. Children's Hospital of Michigan
4. Children's Hospital of Orange County
5. Children's Hospital of Philadelphia
6. Christus Children's Hospital
7. Medical University of South Carolina
8. Nationwide Children's Hospital
9. Texas Children's Hospital
10. University Hospitals Rainbow Babies & Children's
11. University of California, Davis Health
12. University of Pittsburgh
13. University of Utah Health
14. Virginia Commonwealth University

To strengthen recruitment, we have selected CPCCRN sites with strong research infrastructures and patient diversity, as well as investigators with extensive clinical and research experience with children and families in the PICU. This will take advantage of CPCCRN's proven ability to recruit patients in prior PICU studies, and the already-established infrastructure of the network (see Facilities).

Feasibility of Recruitment

The use of 14 sites will provide ample patient volume to facilitate successful recruitment. CPCCRN has proven an outstanding source of recruitment for a diverse set of PICU patients in prior multi-site studies. Dr. Traube, who is the contact Principal Investigator (PI) for this grant, is a senior PICU attending and experienced clinical researcher who has a proven track record of successfully enrolling subjects in other clinical studies. Based on prior annual admissions for ARF, we expect >3000 subjects who will meet inclusion criteria. Over 48 months of recruitment, we expect to enroll 644 children. Our recruitment goal will be a highly feasible 1-2 patients per month at each clinical site.

Recruitment Procedures

Study procedures will be centralized at the **Data Coordination Center (DCC)**, which will monitor recruitment across sites. Each site will have a dedicated Clinical Site PI and trained Site Clinical Research Coordinator (CRC) who will manage local recruitment. The MPIs, Program Managers, Clinical Site PIs, and Clinical Site CRC's will have regular Zoom meetings to communicate updates on recruitment and address any recruitment issues.

Following single IRB review and approval, each clinical site will obtain internal IRB acknowledgement and approval to begin enrollment. Research staff will pre-screen all PICU patients for initial eligibility. This will include PICU patients who are: 1) 0-18 years old, 2) with ARF requiring MV, 3) opioid infusion planned or started, and 4) expected duration of MV >48 hours. If a child is eligible, his/her parent will be approached and invited to participate in the study. We intend to enroll children as soon as possible after intubation to test our hypotheses in children who have not already had extensive opioid exposure before randomization.

If a parent confirms his/her interest in participating, s/he will undergo the informed consent process. Details about the consenting process are included in PHS Section 3.1. We will also maintain a list of all parents approached throughout the entire study to record reasons for refusal and avoid approaching people multiple times. This list will be destroyed at the completion of the project. Parents will provide consent to include medical information from their children's electronic medical record. Children who are eight or older who can communicate will also be asked to provide assent. If a child refuses to provide assent, s/he will not be enrolled in the study. The consent form will be signed with the parent's full understanding of the study process.

Enrolled participants will be randomized using a web-based system located at the DCC. Participants will be randomized via a web-based platform utilizing permuted-block randomization, stratified by site, in a 1:1:1:1 allocation across the 4 experimental groups. Overall recruitment tracking, data management, and other study activities will be centralized at the DCC.

Retention:

We will carefully track factors related to participant retention and attrition. We do not expect significant attrition, as study participation ends when the child is discharged from the PICU, and prolonged retention is not needed.

STUDY TIMELINE - OPTICOM

All aims pertaining to human subjects' enrollment, biospecimen collection, and data analysis will be completed during the project period.

We plan on recruiting a total of 644 infants, children, and adolescent patients who are admitted to a Pediatric Intensive Care Unit (PICU) with ARF requiring MV. Participants will be randomized into 4 group with 161 participants in each study group. These groups are: IV-A + Placebo (AO), IV-K + Placebo (KO), IV-A + IV-K (AK) or Placebo + Placebo (OO).

		Year 1												Year 2				Year 3				Year 4				Year 5			
		M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	Q1	Q2	Q3	Q4												
"Optimizing Treatment In Children On Mechanical ventilation" Timeline																													
Pre-Enrollment Period																													
Steering Committee established	X																												
CDEs coordinated with RDC		X																											
Protocol finalized		X																											
IND approved		X																											
Finalize Manual of Operations		X																											
Finalize a Risk Assessment and Mitigation Plan		X																											
Finalize DSMB Charter			X																										
sIRB approval		X																											
Finalize CRFs and Database		X																											
Register Clinicaltrials.gov		X																											
Central Pharmacy Set-Up		X																											
Subawards Executed			X																										
SIRB Reliance Agreements			X																										
Local sIRB Acknowledgement			X																										
Train Site Study Staff			X																										
Implementation of PEDP Plan				X																									
Site Activation					X																								
Enrollment Period																													
Steering Committee Meetings		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Ongoing Targeted Meetings and Intervention for PEDP											X		X		X		X		X		X		X						
DSMB Meetings			X								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Annual FDA Reporting												X				X			X			X					X		
Executive Team Meetings (HEAL-KIDS)	X		X									X				X			X			X					X		
Publication Plan Finalized													X																
Enrollment Targets																													
First Participant Enrollment													X																
25% target enrollment															X														
50% target enrollment																	X												
75% target enrollment																						X							
Last Participant Enrolled																												X	
Post-Enrollment Period																													
Data Entry Complete																									X				
Database Cleaning																								X					
Statistical Analysis																												X	
Manuscript Submission																												X	
Public Use Dataset (Including CDEs) Published to HEAL-KIDS																												X	

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
<u>Study 1, IER 1</u>	Domestic	14 clinical sites in the USA through the CPCCRN Network

Inclusion Enrollment Report 1

1. Inclusion Enrollment Report Title* : Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)
2. Using an Existing Dataset or Resource* : Yes No
3. Enrollment Location Type* : Domestic Foreign
4. Enrollment Country(ies): USA: UNITED STATES
5. Enrollment Location(s): 14 clinical sites in the USA through the CPCCRN Network
6. Comments:

Planned

Racial Categories	Ethnic Categories				Total	
	Not Hispanic or Latino		Hispanic or Latino			
	Female	Male	Female	Male		
American Indian/ Alaska Native	4	5	1	2	12	
Asian	15	17	4	5	41	
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	
Black or African American	81	102	24	30	237	
White	109	139	33	41	322	
More than One Race	11	14	3	4	32	
Total	220	277	65	82	644	

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total	
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity				
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported		
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0	
Asian	0	0	0	0	0	0	0	0	0	0	
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0	
Black or African American	0	0	0	0	0	0	0	0	0	0	
White	0	0	0	0	0	0	0	0	0	0	
More than One Race	0	0	0	0	0	0	0	0	0	0	
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0	
Total	0	0	0	0	0	0	0	0	0	0	

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects [Protection_of_Human_Subjects.pdf](#)

3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?

Single IRB plan attachment

3.3. Data and Safety Monitoring Plan [Data_and_Safety_Monitoring_Plan.pdf](#)

3.4. Will a Data and Safety Monitoring Board be appointed for this study?

3.5. Overall structure of the study team [Overall_Structure_of_the_Study_Team.pdf](#)

3. PROTECTION OF HUMAN SUBJECTS - OPTICOM

3.1 RISKS TO HUMAN SUBJECTS

3.1.1. Overall Study Design

The Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM) study is a double blind randomized controlled trial (RCT) designed to test the effects of intravenous acetaminophen (IV-A) and/or intravenous ketorolac (IV-K) at reducing pain in children with acute respiratory failure (ARF) on invasive mechanical ventilation (MV). Eligible consented patients will be randomized equally into one of four arms: IV-A + Placebo (AO), IV-K + Placebo (KO), IV-A + IV-K (AK) or Placebo + Placebo (OO). The primary outcome is reduction of acute pain in the first 5 days of MV. Secondary outcomes include reduction in opioid exposure, opioid withdrawal, delirium, and duration of MV.

3.1.2 Subject Population to be Studied.

Participating sites will enroll infants, children, and adolescent patients who are admitted to a Pediatric Intensive Care Unit (PICU) with ARF requiring MV. The goal is to determine if adding adjuvant non-opioid analgesics (specifically, IV-A and IV-K) will reduce acute pain. Inclusion Criteria and Exclusion Criteria are listed in the Table below:

Inclusion Criteria	Exclusion Criteria
Age ≤ 18 y	Tight temperature control required for clinical care
ARF requiring endotracheal intubation	Contraindications to IV-A
Ability to approach family and obtain consent within 6 h of endotracheal intubation	Contraindications to IV-K
Opioid infusion planned/started	Requirement for prolonged neuromuscular blockade
Expected duration of MV of > 48 h	Known pregnancy
	Unwillingness of clinical team to allow randomization
	Prior enrollment in the OPTICOM Trial

3.1.3 Procedures for Assignment to Study Group

Immediately after consent, randomization will occur using a web-based system located at the Data Coordinating Center (DCC). Participants will be randomized via a web-based platform utilizing permuted block randomization, stratified by site, in a 1:1:1:1 allocation across the 4 experimental groups.

3.1.4 Anticipated Numbers of Subjects for Each Study Group

A total of 644 participants will be randomized, with 161 participants in each study group. The basis of the application is a 2 x 2 factorial RCT, as the most efficient way to test the effect of two distinct treatments. The two primary analyses will be a comparison of those with versus without IV-A (AO/AK versus KO/OO) and a comparison of those with versus without IV-K (KO/AK versus AO/OO). This design will allow us to evaluate both IV-A and IV-K for very little additional cost or complexity compared with testing only one intervention. Additionally, this approach provides the ability to evaluate possible interaction between acetaminophen and ketorolac.

3.1.5 Collaborating Sites Performing the Research

All of the collaborating sites are tertiary or quaternary pediatric intensive care units in large academic health centers or children's hospitals (shown in Table below). The patients who are eligible for participation in OPTICOM are all critically ill children with ARF, and require 24 hour care in the PICU by pediatric critical care physicians, nurses, respiratory therapists, and other clinical staff.

Clinical Site	Site Contact PI
Arkansas Children's Hospital	Ronald Sanders, MD
Children's National Medical Center	Michael Bell, MD
Children's Hospital of Michigan	Kathleen L. Meert, MD

Children's Hospital of Orange County	Adam J. Schwarz, MD
Children's Hospital of Philadelphia	Heather Wolfe, MD
Christus Children's	Mohammad K. Salameh, MD
Medical University of South Carolina	John Costello, MD, MPH
Nationwide Children's Hospital	Mark W. Hall, MD
Texas Children' Hospital	Ayse Akcan-Arikan, MD
University Hospitals Rainbow Babies & Children's	Steven Shein, MD
University of California, Davis Health	Moonjoo Han, MD
University of Pittsburgh	Joseph Carcillo, MD
University of Utah Health	Jill Sweeney, MD
Virginia Commonwealth University	Nikki Miller Ferguson, MD

The University of Utah, located at the DCC, will serve as the single IRB for the participating sites. All tasks related to IRB and study management will be led by the MPIs (Traube, Bell & Holubkov). Clinical supervision will be centralized at the DCC. Clinical site PIs will be responsible for overseeing local recruitment and research activities.

3.1.6 Study Procedures, Materials, and Potential Risks

Study Procedures

Patients will be screened by site research staff, and if eligible, their parents will be approached as soon as possible after intubation for permission to participate in the study. Patients whose parents give permission will be randomized by the DCC, with group assignment provided to the investigational pharmacy at the clinical site. The site's investigational pharmacy will provide the proper blinded study drug to the subject's bedside for infusion. Based on randomization (AO, KO, AK, OO), the patient will receive one of the following dosing regimens:

Group	IV Acetaminophen Dose	IV Ketorolac Dose
AO	15 mg/kg* (maximum 600 mg) every 6 h	Placebo (IV 0.9% NSS) every 6 h
KO	Placebo (IV 0.9% NSS) every 6 h	0.5mg/kg (maximum 30 mg) every 6 h
AK	15 mg/kg* (maximum 600 mg) every 6 h	0.5mg/kg (maximum 30 mg) every 6 h
OO	Placebo (IV 0.9% NSS) every 6 h	Placebo (IV 0.9% NSS) every 6 h

*Note: For children <28 days old, IV-A dose will be 12.5 mg/kg every 6 hours, as per FDA recommendations.

Medications will be staggered in such a manner that a medication is administered every 3 hours – active drug or placebo.

All participants will have standard-of-care assessment measures completed by trained PICU nurses. This will include: the Faces, Legs, Activity, Cry, and Consolability (**FLACC**) pain score, which will be measured **every 4 hours** for the first 5 days of MV; the Withdrawal Assessment Tool (WAT) every 4 hours from initiation of opioid taper until PICU discharge; and the Cornell Assessment of Pediatric Delirium (CAPD) every 12 hours for the first 5 days of MV.

Study Materials

Sources of research material will include data normally found in the participant's medical record. This data will be recorded during the participant's PICU stay. We will collect all required demographic information, and granular information regarding opioid use, including: 1) name of opioid, 2) dose of opioid, 3) prescription duration

(specifically, total days exposed), and 4) **MME value, in morphine milligram equivalents per kilogram**, using conversion factors provided by HEAL.

In addition, we will collect the following information specifically for the OPTICOM study, completed by the parent proxy, and in compliance with the Common Data Elements specified in the HEAL-KIDS initiative:

HEAL-KIDS Core Common Data Elements:

	Measure Title	Description of Measure	Time Points	Time (min)
1.	<i>PedsQL Inventory</i>	Describes difficulty associated with carrying out activities requiring physical actions, such as instrumental activities of daily living, as well as problems with psychological state and social interactions	Enrollment	~5
2.	<i>NIDA Modified Assist Tool-2</i>	Screener for unhealthy use of tobacco, alcohol, illicit drugs, and non-medical prescriptions in the past 2 weeks	Enrollment	~5
3.	<i>BPI Pain Severity</i>	Measures magnitude of the pain sensations experienced in the past 24 hours	Study day 2, Study day 4	<2
4.	<i>BPI Pain Interference</i>	Measures the degree to which there are consequences of pain on aspects of a participant's life in the past 24 hours	Study day 2, Study day 4	<2
5.	<i>Pain Catastrophizing Scale for Children</i>	Measures the degree of negative attitudes a parent has towards their child's pain experience	Prior to PICU Discharge	~5
6.	<i>PHQ-2</i>	Measures parent's perception of child's depression symptoms	Prior to PICU Discharge	<2
7.	<i>GAD-2</i>	Measures parent's perception of child's anxiety symptoms	Prior to PICU Discharge	<2
8.	<i>AWS+ Sleep Duration Items</i>	Measures perception of sleep duration	Prior to PICU Discharge	<2
9.	<i>Patient Global Impression of Change</i>	Measures global satisfaction with pain treatment	Prior to PICU Discharge	~5

As per discussion with the HEAL CDE Program Director, for CDEs that are appropriate (i.e.: Pain Interference and Pain Intensity), we will collect measures multiple times during this short window. For others (i.e.: Physical Functioning, Substance Use Screener) we will collect information once, with parent providing a retrospective assessment of baseline functional values as soon as possible after enrollment. Similarly, we will collect the measures for Pain Catastrophizing, Sleep, Depression, Anxiety, and Global Satisfaction with Treatment once, prior to discharge from the PICU. Most importantly, we will have multiple granular measurements of opioid exposure in morphine milligram equivalents (MMEs) as per the CDE definition.

Data will be recorded on worksheets at each clinical site, and then entered into a computerized data system maintained by the DCC. All Protected Health Information will be stored in secure databases and will be associated with an ID number for each participant. The final analysis data sets will be deidentified by the DCC. Parental permission forms will specify that de-identified study data will be made available for other research (as per NIH and HEAL-KIDS criteria) after the OPTICOM study is completed.

Potential Risks of Study Participation

Intravenous Acetaminophen (IV-A)

Intravenous Acetaminophen (IV-A) is FDA-labeled for the treatment of moderate to severe pain with adjunctive opioid analgesics. Although currently labeled for use in adults and children 2 years and older, the FDA provides

dosing guidelines for neonates and infants as well. Recommended dosing is 15 mg/kg q 6 hours, with a single-dose maximum of 1 gram. (For infants <28 days, the FDA recommends 12.5 mg/kg/dose q 6 hours). Acetaminophen is contra-indicated with severe active liver disease, and in patients with known hypersensitivity. When used in doses higher than recommended, there is a risk of hepatic injury. It should be used with caution in patients with severe renal disease (creatinine clearance <30 ml/min), alcoholics, and severely malnourished or severely hypovolemic patients. We do not expect to see these adverse events in the OPTICOM study given the careful inclusion criteria, protocolized approach to dosing (as most complications occur when acetaminophen is over-dosed) and given the short duration of treatment (maximum 20 doses over 5 days). In some pediatric patients, nausea, vomiting, pruritis, and constipation have been described (of note, many of those children were simultaneously taking opioids, which are more strongly associated with these same complications). Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been rarely reported.

Intravenous Ketorolac

Intravenous Ketorolac (IV-K) is FDA-labeled for treatment of moderately severe acute pain that requires analgesia at the opioid level. It is FDA-labeled for adult use but is frequently used “off-label” in pediatrics due to its potent analgesic effects and relatively low risk of adverse effects. Recommended dosing in pediatrics is 0.5 mg/kg IV q 6 hours, with a single-dose maximum of 30 mg, and not to exceed 5 days. Ketorolac has been associated with gastrointestinal (GI) side effects, including peptic ulcers, bleeding, and intestinal perforation, especially in geriatric patients, and is contra-indicated in patients with a history of peptic ulcers and/or GI bleeds. In adults, it has been associated with an increased risk of cardiovascular thromboses, but this has not been described in children. It is contra-indicated in patients with severe renal impairment or renal failure, and in pregnant patients. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been rarely reported. Risk of side effects increase when ketorolac is given at higher doses, in combination with other non-steroidal anti-inflammatory drugs, and for prolonged periods of time. We do not expect to see these adverse events in this study given the careful inclusion criteria, protocolized approach to dosing and the short duration of treatment (maximum 20 doses over 5 days).

Loss of Confidentiality

There is a minimal risk of loss of confidentiality for data collected in this study.

Alternatives to Study Participation

Study participation is not required for patients to receive state-of-the-art critical care for ARF. Parents may elect to discontinue study interventions at any time, which will be considered discontinuation of study drug. Data collection will continue unless parents wish to discontinue all study participation. Data that have been collected up to that point will be retained in the study.

3.2 ADEQUACY OF PROTECTION AGAINST RISKS

3.2.1 Parental Permission, Informed Consent and Assent

Subjects who are eligible for this study are under 18 years of age, and written permission will be required from the parent for participation. After determining that a subject is eligible, the site investigator or designee will approach the parent to offer participation for their child in the study. Single parent permission is permitted under 45CFR §46.405. The parent or legal guardian will be informed about the objectives of the study and the potential risks and benefits of their child’s participation. If the parent refuses permission for their child to participate, then all clinical management will continue to be provided by the clinical ICU staff in accordance with institutional practice and judgment.

Subjects who are eligible for this study will be critically ill and intubated, and child assent is typically not possible at the time of study enrollment. However, in the rare instance where the child is capable of giving assent (i.e.: alert and competent), they will be asked, following an age-appropriate discussion of risks and benefits, to give assent to the study. Assent will be waived if the child is too young, has a severely reduced mental age, decreased level of consciousness, psychological problems, or other legitimate reasons as judged by the single IRB and the institution’s specific Human Research Protection program policies.

3.2.2 Institutional Review Board and Human Research Protection

The Institutional Review Board (IRB) at the University of Utah will serve as the single IRB. The Utah IRB has extensive experience with single IRB implementation due to participation in the CPCCRN network. The main protocol will be reviewed separately from each institution, and each participating institution will be approved individually. No human subjects research activities will be conducted at any CPCCRN site prior to sIRB approval at the University of Utah.

In addition to sIRB activities, each institution has Human Research Protection activities that will be completed prior to site activation. These include conflict of interest, assuring competence of investigators, impact on hospital services, etc., and are individualized to each site.

3.2.3 PROTECTIONS AGAINST RISK

Study Drug Risk

All patients in the study have acute respiratory failure, are intubated, and are receiving opioids for pain related to MV. They will all be located in PICUs where they will be closely monitored for changes in clinical status and/or laboratory abnormalities associated with either of the study drugs. Further, the study drug dosing will be tailored to the individual subject's weight, reducing the risk of unintended side effects.

In this study, IV-A is being given at the FDA-labeled weight-based dose for children for a short duration (maximum of 20 doses). Accordingly, we do not expect to see hepatic injury or other adverse events.

Prior studies in children less than 2 years old have demonstrated safety of IV-A, and the Food and Drug Administration (FDA) has approved Investigational New Drug (IND) applications for this population in the past. IV-A is routinely used "off-label" in infants and young children in the PICU. However, as IV-A is not yet FDA-labeled for children less than 2 years old, we are in the process of applying for an IND for the OPTICOM study.

Similarly, in this study, IV-K is also being given at the recommended weight-based dose for children and will be limited to a maximum of 20 doses. Accordingly, we do not expect to see GI side effects, or other adverse effects. Prior pediatric studies, including studies focusing on children less than 6 months old, have demonstrated safety of IV-K, and the FDA has approved IND applications for this population in the past. IV-K is routinely used "off-label" in infants, children, and adolescents. However, as ketorolac is not yet labeled for children less than 17 years old, we are in the process of applying for an IND for the OPTICOM study.

To mitigate risk to patients in the study, OPTICOM has established consistent processes for adverse event reporting and included Dr. Margaret Parker, with >27 years' experience as a PICU Director, who will consult as Medical Monitor. The Medical Monitor will be unblinded to group assignment and will work to ensure that any patient safety concerns are addressed immediately. We will also have a 5member NICHD-appointed Data Safety Monitoring Board (DSMB) that includes expertise in pediatrics and critical care. A detailed DSMB report including adverse events will be generated by the DCC for DSMB meetings.

Breach of Confidentiality

The minimal risk of loss of privacy is mitigated by the substantial data management resources and security described in the Facilities and Resources section of the Data Coordinating Center Component of this application.

Vulnerable Subjects

The OPTICOM study will enroll children < 18 years of age and this is a vulnerable population. The study will be carried out in pediatric intensive care units staffed by board-certified or board-eligible pediatric critical care physicians, and a pediatric clinical team that is specifically trained and expert in the clinical management of critically ill infants, children and adolescents. All clinical sites in CPCCRN are pediatric intensive care units that normally admit patients with acute respiratory failure within the age group of the OPTICOM study.

Research in children involves special protections under 45 CFR §46 Subpart D "Additional DHHS protections for children involved as subjects in research" and 21 CFR §50 and §56. OPTICOM is permissible under these regulations as: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR §46.405).

3.3 Potential Benefits of the Proposed Research

The goal of this study is to reduce acute pain in children with ARF on IMV. Participants will be told that there is no guarantee of benefits to them based on study participation. Children who enroll in this study will have a 75% chance of getting at least one of the study drugs, IV-A and/or IV-K. If either or both of the drugs are effective, there is potential benefit to the participant in terms of reduced acute pain episodes and/or reduced exposure to opioids. For the 25% of patients randomized to the OO group (placebo x 2 with neither IV-A nor IV-K), knowledge gained from their participation in the study may help other children in the future.

3.4 Importance of the Knowledge to Be Gained

More than 24,000 children develop ARF and require MV— an intrusive, painful, lifesaving procedure in the US each year. They universally receive high-dose opioids, yet still experience episodes of acute pain. Studies show that repeated episodes of acute pain and prolonged opioid exposure put children at risk for chronic pain, opioid tolerance, withdrawal, delirium, and other negative effects. Yet, few randomized controlled trials target optimizing acute pain management in children with ARF on MV. The primary objective of the OPTICOM study, based on substantial preliminary work, is to define the effectiveness of supplementing opioids with protocolized acetaminophen and/or ketorolac at decreasing episodes of acute pain in this high-risk population. The OPTICOM study will advance the treatment of acute pain in a diverse population of children across the age spectrum and advance our ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with ARF.

DATA AND SAFETY MONITORING PLAN - OPTICOM

1. Data Collection, Monitoring, and Oversight

The OPTICOM clinical study will be overseen by the Data Coordinating Center (DCC), located at the University of Utah. The study MPIs, Drs. Traube, Bell, and Holubkov, will be responsible for overseeing activities at all recruitment sites.

The University of Utah Institutional Review Board (IRB) will serve as the single IRB. The Utah IRB has extensive experience with single IRB implementation, as described in the **Facilities**. No human subjects research activities will be conducted at any OPTICOM site prior to receiving sIRB approval from the University of Utah.

The DCC will perform Good Clinical Practice (GCP) and study-specific training prior to study initiation at each study site. Additional trainings will be performed as needed throughout the study.

All study staff will be CITI-trained. All participant data will be identified via a study ID that will serve as the link to identifiable information at each site. The linking list will be stored in a password-protected location, and any hard copies of collected data will be kept in a locked file cabinet within a locked office and will only be accessible to the study PI and appropriate staff members.

Data will be collected by the site research coordinators by entering data directly into REDCap, which is a secure, internet-based data capture and management system. We will maintain the confidentiality of data within REDCap by associating participant data only with each participant's unique study ID number. Members of the research team will complete study forms, and these forms will be stored electronically on the secure REDCap system. Any participant inquiries or concerns about the database will be directed to Dr. Holubkov or Dr. Reeder, both DCC investigators.

The DCC will be responsible for monitoring this study using a risk-based approach to monitoring, as described in detail in the **Facilities**. The trial PIs are ultimately responsible for the conduct and monitoring of the trial. Study monitoring includes auditing of selected cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance. Study drug accountability will be also be monitored using a risk-based approach.

The DCC will review data collection forms on an ongoing basis for data completeness and accuracy, as well as protocol compliance. The DCC data manager will write missing data, consistency, and logic checks into the REDCap data forms. In addition, the DCC has developed a Query Management System that has been used for more than 20 years (see **Facilities**). The DCC data manager will develop rules for each data element, and will write SQL queries to enforce each rule. The Query Management System executes nightly, identifies new discrepancies, and creates and sends an email to each site research coordinator containing all new discrepancies. If a discrepancy is corrected in REDCap by the site research coordinator, the query will automatically resolve. Communication between the DCC data manager and site research coordinator is carried out within the system, so a complete audit trail is available for all data element changes and query resolutions.

Participant accrual rate and compliance with inclusion/exclusion criteria will be reported regularly during monthly meetings. Research staff will collect data on and review adherence to the treatment protocol during the intervention.

Monitoring plans and reporting requirements will be reviewed during the study orientation at all sites before recruitment begins. Regular video meetings with all sites, led by the study PI(s) and the DCC will serve to ensure that all proper protocols are followed. The DCC uses both remote and onsite data monitoring, as appropriate and as specified in the Risk-Based Monitoring Plan that will be created for the OPTICOM study.

2. Data Safety Monitoring Board (DSMB)

The Steering Committee will recommend individuals with expertise to serve on the DSMB, and the DSMB will be formally approved or appointed by NICHD. Suggested members will include a pediatric intensivist, a biostatistician, and a clinical ethicist. The anticipated size of the DSMB is five members. Members of the DSMB will not have any affiliation with the University of Utah, or any of the collaborating clinical sites involved in

CPCCRN. Drs. Traube and Holubkov have first-hand experience serving as members of DSMBs for clinical trials, and both investigators have chaired a DSMB. Dr. Holubkov also has over thirty years of first-hand experience leading DSMB meetings as the DCC PI. Our proposal for DSMB function reflects this experience, though we thoroughly understand that all aspects of DSMB operations will be approved by NICHD.

The DSMB will meet once prior to the start of the OPTICOM study, and will approve the final protocol prior to implementation. The DSMB will also establish and approve a charter to guide its function for the trial. The DSMB charter will be drafted by the Data Coordinating Center to facilitate this step. The charter will include rules of procedure, definitions of a meeting quorum, and information about meeting logistics. The initial meeting will also include detailed explanation of the study design including recommended monitoring boundaries for interim analyses. After the DSMB has approved its charter and the final protocol, the Data Coordinating Center will send this information to the single Institutional Review Board at the University of Utah. The notice of DSMB approval will also be sent to each collaborating site to facilitate the Human Research Protection (HRP) activities that need to be accomplished in addition to the single IRB approval of the study.

The purpose of the DSMB is to advise the Federal funding agency (NICHD) and trial leadership regarding the continuing safety of study participants and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring study participant accrual, protocol adherence, data quality assessments, individual clinical site performance, serious adverse event review, and other participant safety issue review. The Data Coordinating Center will send reports relating to these topics to DSMB members ten days prior to each DSMB meeting. We propose that the DSMB will meet three times annually during patient accrual into the study, although the DSMB will have the discretion to alter meeting timing and frequency. These meetings may be held in person if warranted, but we anticipate meetings will be held via webinar.

DSMB meetings to evaluate study protocols, prior to study implementation, may be open or closed according to the decision of the DSMB members. We suggest that these meetings should be open to members of the trial leadership team, as there are no confidential components to these proceedings, and it will facilitate the review and appropriate alterations of the protocol in response to DSMB concerns.

DSMB meetings during study enrollment are often conducted with an initial open session that may include investigators, NICHD staff, and the DSMB. During this open session, general information about the study is provided, alterations to the DSMB charter may be discussed, and general information about study progress may be presented by the Data Coordinating Center. For example, information about overall patient accrual might be provided. All information provided in the open session is public information. The second session, involving presentation and discussion of confidential study data, should be open only to the DSMB and the Data Coordinating Center biostatisticians (Dr. Holubkov and/or Reeder). The third session is an executive session restricted to DSMB members, during which recommendations for study continuation are debated and finalized. The fourth and final session may be a debriefing session open to DSMB members, NICHD, and Data Coordinating Center staff. The latter session is optional, as NICHD may prefer that the DSMB send its recommendations directly to the Program Officer and not hold a debriefing session with investigators.

In the unlikely event that the DSMB recommends emergent cessation of enrollment because of safety concerns, this communication will be made on the same day as the DSMB meeting to the DCC PI. This is highly unlikely because adverse events will be continually assessed by the Medical Monitor, who already has authority to emergently suspend enrollment without DSMB involvement. If emergent cessation is recommended, NICHD, FDA, and trial leadership will be notified by the DCC.

The Data Coordinating Center will staff DSMB meetings and produce minutes of the meetings for MPIs. Closed session minutes will be confidential to the DSMB until the study is completed. Open session minutes will be available to the NICHD and trial leadership after DSMB Chair approval.

3. Adverse Event Reporting

Consultant and Medical Monitor, **Margaret Parker, MD**, has served on the Steering Committee of the Surviving Sepsis Campaign for the initial development and first revision of the guidelines, as well as on the Pediatric Surviving Sepsis Guideline Task Force and will review study design prior to initiation of enrollment, review any serious adverse events,

provide medical support to clinical sites and project team, and attend steering committee meetings as needed. This review will be timely so as to meet the requirements for adverse event reporting detailed below.

3.1 Definitions, Relatedness, Severity and Expectedness

An adverse event (AE) is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom.

The clinical site investigator will evaluate adverse events. Adverse events not previously documented in the study will be recorded on the adverse event record form. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment should be established.

The suspected relationship between study intervention and any adverse event will be determined by the clinical site investigator using the following criteria:

Not Related: The event is clearly related to other factors, such as the participant's clinical state, therapeutic interventions, or concomitant drugs administered.

Possibly Related: The event follows compatible temporal sequence from the time of administration of study drug, but could have been produced by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs administered.

Probably Related: The event follows a reasonable temporal sequence from the time of study drug administration, and cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs administered.

The seriousness of clinical adverse events and laboratory abnormalities will be recorded by the clinical site investigator and categorized. A serious adverse event (SAE) is an adverse event that:

- is fatal; or
- is life-threatening (the patient was, in the view of the clinical site investigator, in immediate danger of death from the event as it occurred); or
- is severely or permanently disabling; or
- necessitates significant intervention, such as major surgery, to prevent permanent impairment of a body function or permanent damage to a body structure; or
- requires or prolongs hospitalization (An elective hospitalization for a planned procedure will not be considered an adverse event and reporting is not required); or
- the clinical site investigator considers it to be a serious adverse event.

All adverse events will be evaluated as to whether their occurrence was expected or unexpected. An adverse event is considered expected if it is known to be associated with the underlying medical condition of the subject, is directly related to study outcome, or is otherwise mentioned in the protocol, informed consent, drug package inserts, or other study documents.

For each adverse event, the clinical site will record whether an intervention was required:

- Intervention: Surgery or procedure
- Other Treatment: Medication initiation, change, or discontinuation
- None: No action taken

Finally, the clinical site will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae
- Symptoms continue

3.2 Data Collection Procedures for Adverse Events

After patient enrollment, all adverse events, whether anticipated or unanticipated, will be recorded according to the date and time of first occurrence, seriousness, and their duration, as well as any treatment prescribed. Any medical condition present at the time of enrollment, recorded in the patient's baseline history at study entry, which remains unchanged or improves, will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the initial evaluation will be considered a new adverse event and reported.

Abnormal laboratory values that are clinically significant will be recorded as adverse events and the clinical site investigator will assess the seriousness and relationship to the study. Laboratory values that are abnormal at study entry and that do not worsen will not be recorded as adverse events.

Adverse events will be coded using the MedDRA coding vocabulary. The Data Coordinating Center has experience with MedDRA. Coding will be done centrally at the Data Coordinating Center because this requires specific training.

3.3 Monitoring Serious Adverse Events

Dr. Parker will act as the medical monitor for the OPTICOM study. Clinical site investigators or coordinators will report all serious adverse events to the Data Coordinating Center within 24 business hours after they become aware of the event, and the medical monitor will assess all serious adverse events reported from clinical sites. For each serious adverse event, the clinical site will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. All SAE reports will be retained at the Data Coordinating Center, and all SAE reports will be available for review by the DSMB and NICHD.

In the unlikely event that the medical monitor believes an SAE warrants emergent cessation of enrollment in the trial, the trial leadership and the DCC PI will be immediately notified. If there is concurrence after discussion, the Data Coordinating Center will notify all clinical site investigators to cease enrollment in the trial. The chair of the DSMB will also be notified. Resumption of enrollment will not occur without consent of the DSMB, NICHD, FDA, and study investigators.

3.4 Reporting Procedures

Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. All adverse events will be evaluated by the Principal Investigator, and will be classified as noted previously. All adverse events occurring within the study period will be recorded and entered into the system provided by the Data Coordinating Center.

The clinical site investigator will report all serious adverse events to the Data Coordinating Center within 24 hours. The Data Coordinating Center will report all serious, unexpected, and study-related adverse events to trial leadership, the NICHD, the FDA, and the Data Safety Monitoring Board (DSMB), within 7 calendar days of receiving the report from the clinical site. A written report will be sent to the NICHD and FDA within 15 calendar days and these reports will be sent to the Institutional Review Board in Utah as well as each institution's Human Research Protection program. The DSMB will also review all adverse events (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings.

3.5 Post-Study Adverse Events

All unresolved adverse events at the time of the participant's termination from the study will be followed by the investigators until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained or has stabilized. At the time of discharge from the pediatric intensive care unit, the investigator will instruct each parent to report any subsequent event(s) which the parent, or the participant's personal physician, believes might reasonably be related to participation in this study. Any death or other clinically serious adverse event that may be related to the study, and that occurs at any time after a participant has discontinued or terminated study participation will be reported.

4. Unanticipated Problems

Incidents or events that meet the OHRP criteria for unanticipated problems require reporting similar to adverse event reporting. Unanticipated problems meet all of the following criteria:

- Unexpected in terms of nature, severity or frequency given the research procedures and the characteristics of the subject population;
- Related or probably related to participation in the study;
- Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

5. Institutional Review Board (IRB) Reporting

Unexpected SAEs that are judged to be related to participation in the trial will be reported to the single IRB at Utah and each clinical site Human Research Protection program.

On an annual basis, the DSMB report indicating approval to continue the study will be provided to each participating clinical center, and the single IRB in Utah. This DSMB recommendation is based on DSMB examination of all SAEs that have been reported in the trial, review of interim reports, and ongoing validity and scientific merit of the trial.

6. Certificate of Confidentiality

NIH will automatically issue a Certificate of Confidentiality to protect against the compelled disclosure of personally identifiable information and to support and defend the authority of the Certificate against legal challenges. University of Utah (UU), Weill Cornell Medicine (WCM), and personnel involved in the conduct of research will comply with all applicable federal regulations for the protection of human subjects. This Certificate of Confidentiality will not be represented as an endorsement of the project by the DHHS or NIH or used to coerce individuals to participate in the research project. All participants will be informed that a Certificate has been issued, and they will be given a description of the protection provided by the Certificate.

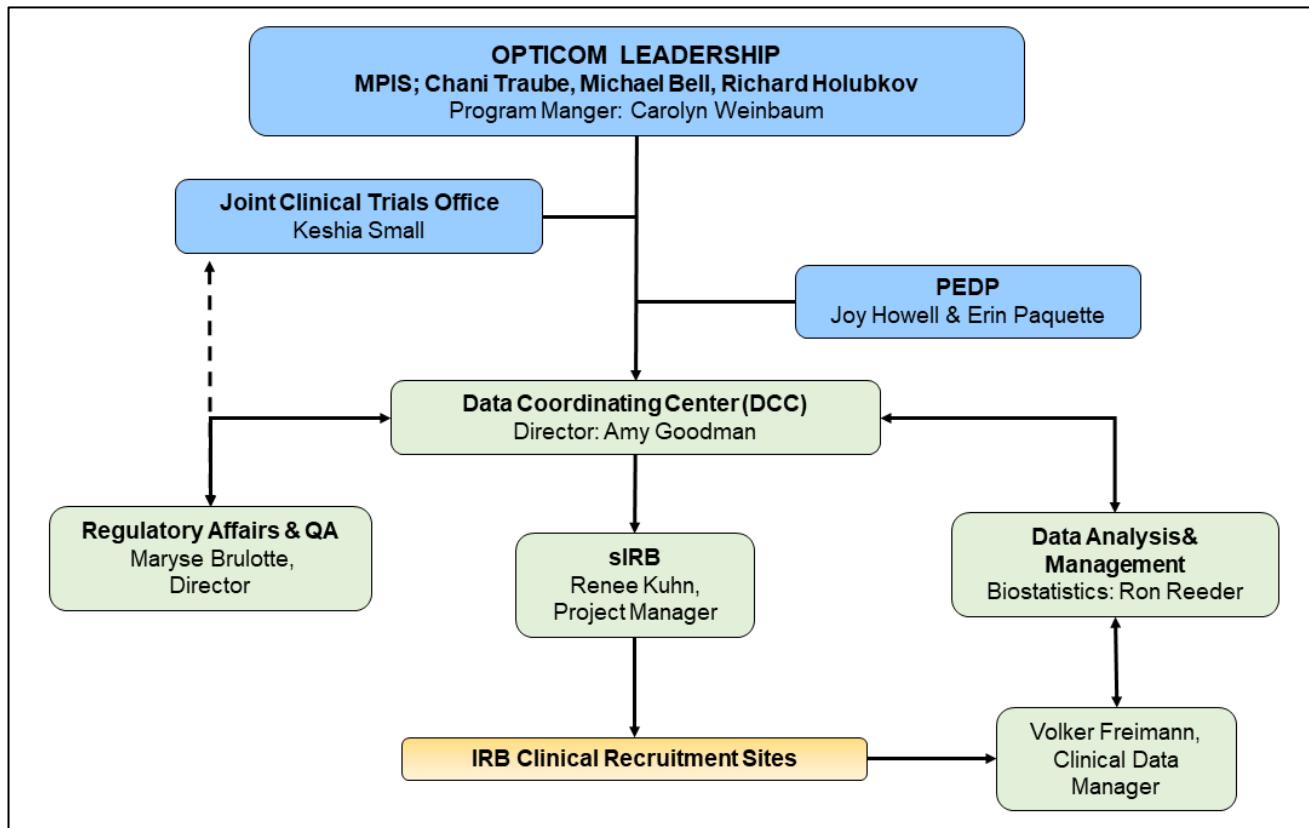
7. ClinicalTrials.gov

The OPTICOM project includes an applicable clinical trial, which will require registration on ClinicalTrials.gov. If funded, the study will be registered on ClinicalTrials.gov.

TEAM STRUCTURE - OPTICOM

The OPTICOM clinical study will be overseen through the Data Coordinating Center (DCC), located at the University of Utah. The study MPIs, **Drs. Traube, Bell, and Holubkov**, will be responsible for overseeing activities at all recruitment sites.

Additional Clinical Team Members include the following:



Joy Howell, MD, is Assistant Dean for Diversity and Student Life at Weill Cornell Medicine, Vice Chair for Diversity in the Department of Pediatrics, and Professor of Clinical Pediatrics at Weill Cornell Medicine. Dr. Howell will oversee and advise on the **Plan for Enhancing Diverse Perspectives**, and will educate study staff on the history of racism in pain management, and strategies to minimize implicit bias.

Erin Paquette, MD is Associate Professor of Pediatrics at the Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine and Northwestern University Pritzker School of Law. Dr. Paquette is a Bioethicist whose research expertise involves evaluating disparities in research enrollment and participation. She will be responsible for advising on the **Plan for Enhancing Diverse Perspectives**, specifically overseeing approach to patient consent processes to maximize enrollment of a diverse clinical population.

Carolyn Weinbaum, OPTICOM Program Manager leads the Department of Pediatrics Program Management Team (PMT) and will support Dr. Traube and the MPIs by providing oversight for all operations, serving as a conduit for communications, monitoring progress toward scientific milestones, overseeing program and administrative staff (see below), liaising with the Research Business Office (RBO), coordinating meetings, and supervising intellectual property and regulatory compliance.

Keshia Small, MPH Regulatory Research Coordinator, is a senior member of the Joint Clinical Trials office at Weill Cornell Medicine and has been working closely with Dr. Traube (contact MPI) for several years. She will assist the Project Manager with all regulatory paperwork and provide overall support of regulatory compliance and reporting, safety, and ethics reviews, as well as coordination with the CTSC as needed.

Amy Goodman, PhD, DCC Director will oversee all DCC activities and the DCC budget. She will establish and ensure consistent communication with the Principal Investigators and overall Program Manager and assure that the DCC team is functioning efficiently to support the project. She will work closely with the Director of Regulatory Affairs and Quality Assurance to ensure regulatory requirements are addressed.

Renee Kuhn, Project Manager, will be responsible for interfacing with the site personnel, managing the reliance and SIRB process, tracking regulatory documents, assisting with protocol and study document development, and working with the Clinical Data Manager to assure high quality data submission.

Ron Reeder, PhD, Biostatistician, will be responsible for oversight of the proposed investigation at the DCC. He will serve as the primary statistical contact and will direct the efforts of the DCC to provide data management and statistical support for the proposed study.

Volker Freimann, Clinical Data Manager will be responsible for identifying the data variables from the study protocol. He will also develop the database plan and create the electronic data capture system that sites will use to enter the data. He will be responsible for day-to-day monitoring of data submitted from the individual sites.

Maryse Brulotte, Director, Regulatory Affairs and Quality Assurance will assist the project managers with completion of the risk assessment and risk management plan for the OPTICOM study. Ms. Brulotte has assisted in the preparation of many risk management plans and has extensive regulatory experience. She will regularly monitor and update the DCC's risk plan as needed to reflect federal and international regulations.

Participating Clinical Sites:

Clinical Site	Investigator
Arkansas Children's Hospital	Ron C. Sanders, Jr, MD, MS, FAAP, FCCM
Children's National Medical Center	Michael Bell, MD
Children's Hospital of Michigan	Kathleen Meert, MD
CHOC - Children's Hospital of Orange County	Adam J. Schwarz, MD
CHOP - Children's Hospital of Philadelphia	Robert A. Berg, MD, MCCC, FAAP, FAHA
Christus Children's	Mohammad K. Salameh, MD
MUSC - Medical University of South Carolina	John Costello, MD, MPH
Nationwide Children's Hospital	Mark W. Hall, MD, FCCM
Texas Children's Hospital	Ayse Akcan-Arikan, MD
University Hospitals Rainbow Babies & Children's	Steven L. Shein, MD
University of California, Davis Health	Moonjoo Han, MD
University of Pittsburgh	Joseph Carcillo, MD
University of Utah Health	Jill Sweney, MD, MBA
VCU - Virginia Commonwealth University	Nikki Miller Ferguson, MD

Adding/Dropping Clinical Sites:

Dropping sites. There are several reasons why we may need to drop a site from a study. This might include: (a) unresponsive site PI, (b) site PI leaving for a different institution with no identified replacement, (c) unsupportive information technology services, (d) site-level changes in clinical practice such that the site is unlikely or unable to recruit, (e) personal or scientific misconduct, (f) poor recruitment, (g) poor retention, or (h) repeated failure to follow study protocols. We recognize that dropping a site is a fraught decision, given the

loss of institutional prestige of federal research funding and the potential negative impact on personal relationships. A decision to drop a site will be made by a majority vote in the leadership core.

Adding sites. If additional sites are required to complete the study, we would select from among additional members of **CPCCRN Network**. The addition of a new site will be contingent on the identification of a suitable study team, availability of funds, and approval by a vote among the leadership core

Section 4 - Protocol Synopsis (Study 1)

4.1. Study Design

4.1.a. Detailed Description

The Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM) study is a double-blind randomized controlled trial (RCT) designed to test the effects of intravenous acetaminophen (IV-A) and/or intravenous ketorolac (IV-K) at reducing pain in children with acute respiratory failure (ARF) on invasive mechanical ventilation (MV). Eligible consented patients will be randomized equally into one of four arms: IV-A + Placebo (AO), IV-K + Placebo (KO), IV-A + IV-K (AK) or Placebo + Placebo (OO). The primary outcome is reduction of acute pain in the first 5 days of MV. Secondary outcomes include reduction in opioid exposure, opioid withdrawal, delirium, and duration of MV.

4.1.b. Primary Purpose

Treatment

4.1.c. Interventions

Type	Name	Description
Drug (including placebo)	Acetaminophen	IV dose, 15 mg/kg* (maximum 600 mg) every 6 h for 5 days; *Note: For children <28 days old, dose will be 12.5 mg/kg every 6 hours, as per FDA recommendations.
Drug (including placebo)	Ketorolac	IV dose; 0.5mg/kg (maximum 30 mg) every 6 h for 5 days

4.1.d. Study Phase

Phase 3

Is this an NIH-defined Phase III Clinical Trial?

Yes No

4.1.e. Intervention Model

Factorial

4.1.f. Masking

Yes No

Participant Care Provider Investigator Outcomes Assessor

4.1.g. Allocation

Randomized

4.2. Outcome Measures

Type	Name	Time Frame	Brief Description
Primary	Acute Pain Episodes	1-5 days	Number of acute pain events per patient during the first 5 days of mechanical ventilation (MV).
Secondary	Opioid exposure	1-5 days	Opioid exposure will be quantified in morphine milligram equivalents per kilogram during the first 5 days of MV.
Secondary	Withdrawal incidence	1-365 days	Number of patients who develop symptoms of opioid withdrawal during the course of their hospitalization
Secondary	Delirium incidence	1-365 days	Number of patients who develop symptoms of delirium during the course of their hospitalization
Secondary	Length of Invasive Mechanical Ventilation	1-365 days	Length of MV will be measured in hours.

4.3. Statistical Design and Power

Statistical_Design_and_Power.pdf

4.4. Subject Participation Duration 5 days

4.5. Will the study use an FDA-regulated intervention? Yes No

4.5.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/Investigational Device Exemption (IDE) status
Investigational_New_Drug.pdf

4.6. Is this an applicable clinical trial under FDAAA? Yes No

4.7. Dissemination Plan Dissemination_Plan.pdf

4.3. STATISTICAL DESIGN AND POWER - OPTICOM

Overview of Study Design: The basis of the application is a 2 x 2 factorial randomized controlled trial (RCT) of intravenous acetaminophen (IV-A) and/or ketorolac (IV-K) to reduce acute pain. A factorial design was chosen as the most efficient way to test the effect of two distinct treatments. The two primary analyses will be a comparison of those with versus without IV-A (AO/AK versus KO/OO) and a comparison of those with versus without IV-K (KO/AK versus AO/OO). This design will allow us to evaluate both IV-A and IV-K for very little additional cost or complexity compared with testing only one intervention. Additionally, this approach provides the ability to evaluate possible interaction between acetaminophen and ketorolac.

Randomization: Participants will be randomized to acetaminophen vs. placebo as well as to ketorolac vs placebo, creating 4 treatment arms. Participants will be randomized via a web-based platform utilizing permuted-block randomization, stratified by site, in a 1:1:1:1 allocation.

We will examine and report baseline characteristics of the population randomly assigned to the 4 treatments (AO, KO, AK, OO). Means, standard deviations, medians, and inter-quartile ranges will be used for continuous characteristics (e.g., age) while percentages will be used for categorical variables (e.g., sex).

Aim 1: Pain scores will be assessed every 4 hours from randomization until 5 days post-randomization (or extubation if the patient is extubated prior to 5 days). The primary study outcome, number of acute pain events (FLACC score ≥ 4), will be analyzed with a multivariable Poisson regression model. The two exposures are acetaminophen (IV-A vs placebo) and ketorolac (IV-K vs. placebo). Pediatric Risk of Mortality III (PRISM III), a measure of severity of illness, will be included as a covariate in the model to improve fit and increase precision of estimates. PRISM will be calculated with measurements within 2 hours prior to PICU admission through 4 hours after PICU admission or randomization, whichever comes first, to ensure treatment assignment cannot influence PRISM. We will estimate the relative number (rate ratio) of acute pain events with versus without acetaminophen as well as with versus without ketorolac. This ratio will additionally be scaled to the average duration of ventilation [up to 5 days] for interpretation. Incorporating both exposures (IV-A and IV-K, each vs placebo) into a single model provides more precise estimates of each drug's effect by controlling for the other. An offset term in the model will account for varying durations of mechanical ventilation, and a robust error estimator will account for over- or under-dispersion. While we expect approximate additivity of IV-A and IV-K effects (since the mechanisms of action are independent), we will initially fit a model including an IV-A/IV-K interaction term and evaluate its statistical significance. If not significant, we will report effects/significance of each drug from a model without an interaction term; if there is (unexpected) significant interaction, our primary interest will be the effects of each treatment at each "level" of the other (i.e, reporting and contrasting outcomes in the 4 treatment strata). Recognizing power to detect a statistically significant interaction is limited, outcomes in the 4 treatment groups will be reported in all instances.

We will conduct a comprehensive analysis to explore potential variations in treatment effects across key subgroups and across a range of individual risk profiles. Variations across key subgroups (e.g.: age, etiology of ARF) will be evaluated with an effect modeling strategy. The trial's statistical power may be constrained when it comes to detecting disparities in treatment effects among these subgroups. Therefore, we will complement our analysis by assessing the heterogeneity of treatment effects through a risk modeling approach. In this risk modeling approach, our initial step will involve developing a multivariable regression model to predict the number of acute pain events experienced by participants. This model will exclusively use pre-randomization covariates, without consideration of treatment assignment. This model will provide an estimated "risk" score for each participant prior to their randomization into treatment groups. Subsequently, we will employ a second model to evaluate the impact of treatment across a continuous risk spectrum. This will be achieved by incorporating an interaction term that accounts for the treatment group and the estimated pre-randomization risk, allowing us to gauge treatment effects across a wide range of individual risk profiles.

Aim 2: The Aim 2 outcome is cumulative opioid exposure. Cumulative opioid exposure will be calculated as per HEAL CDE standards, in MME/kg, and analyzed with a multivariable linear regression model. To reduce skewness of the distribution and to improve model fit, a log transformation, $\ln(x)$, will be applied to cumulative opioid exposure prior to modeling.

Analogously to Aim 1, the two exposures are acetaminophen and ketorolac. Strategy for evaluation of possible interaction will be analogous to Aim 1; if there is not significant interaction, we will estimate the relative amount of opioid exposure for participants with versus without acetaminophen and with versus without ketorolac. This will be reported as the ratio of geometric means.

Aim 3: Aim 3 outcomes include opioid withdrawal, delirium, and length of mechanical ventilation. Withdrawal will be assessed twice every 4 hours from initiation of opioid taper until discharge from ICU. Delirium will be assessed twice daily from randomization until 5 days post-randomization or extubation. Length of mechanical ventilation (in hours) will be assessed from randomization until extubation.

Opioid withdrawal and delirium will be binary outcomes based on occurrence at any time. Each will be analyzed with separate multivariable Poisson regression models with robust error estimates. Analogous to Aim 1, the two exposures are acetaminophen and ketorolac. We will estimate the relative risks of opioid withdrawal and delirium with versus without acetaminophen and with versus without ketorolac.

Length of MV will be analyzed with a multivariable linear regression model. Analogous to Aim 1, the two exposures are acetaminophen and ketorolac. We will estimate the relative length of MV for participants with versus without acetaminophen and with versus without ketorolac. This will be reported as the ratio of geometric means. To reduce skewness of the distribution and to improve model fit, a log transformation, $\ln(x)$, will be applied to length of MV prior to modeling.

Intention to Treat: Primary analyses for all 3 aims will be conducted according to the intention to treat principle, e.g. all randomized participants will be included based on the treatment to which they were randomized. However, we recognize that oral formulations of acetaminophen or ibuprofen may be given for fever management. In an additional exploratory analysis, we will account for the potential effect of cumulative acetaminophen exposure (oral and intravenous formulations) during the study period in place of randomized to acetaminophen (yes, no).

SAMPLE SIZE AND POWER: Enrolling 644 total participants (161 in each of 4 arms) will provide **90% power** to detect the following outcomes:

- 1) Twenty-five percent reduction in average number of acute pain events (from 7 to 5.3, based on standard deviation of 6.1) during the intervention study period.
- 2) 21% relative reduction in cumulative opioid exposure (based on standard deviation of 0.84 for log-transformed cumulative opioid exposure);
- 3) 14% absolute reduction in opioid withdrawal (from 43% to 29%);
- 4) 13% absolute reduction in delirium (from 80% to 67%);
- 5) 18% relative reduction in duration of MV (based on a standard deviation of 0.72 for log-transformed duration of mechanical ventilation).

As we are testing two primary hypotheses, power calculations are based on a two-tailed t-test for independent samples with a conservative type I error rate (α) of **0.025**.

INVESTIGATIONAL NEW DRUG

The **Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)** study will test the effectiveness of two medications, intravenous acetaminophen and ketorolac, to reduce pain and decrease opioid exposure in children on invasive mechanical ventilation.

Intravenous acetaminophen and ketorolac are both FDA-approved and commercially available drugs. However, as FDA-labeling does not include younger children, we are in the process of applying for an IND for the OPTICOM study (FDA Pre Assignment Numbers 168334 and 168336).

DISSEMINATION PLAN - OPTICOM

Dissemination of study results through ClinicalTrials.gov registration and reporting at a minimum will include the following components: The New York Presbyterian Hospital - Weill Cornell Medicine ClinicalTrials.gov administrator will be responsible for handling the ClinicalTrials.gov requirements for this project under the MPIs' oversight. The trial will be registered prior to enrolling the first participant. Informed Consent Documents for the clinical trial will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov. Once a ClinicalTrials.gov record is established, the MPIs will confirm the accuracy of the record content, resolve problems, and maintain records including content updates and modifications. All submitted information will be updated at least once a year. The MPIs will also be responsible for aggregate results reporting and adverse event reporting at the conclusion of the project, and trial results will be submitted no later than one year after the primary completion date. The OPTICOM study will also be registered on the HEAL Data Platform, a single interface where users can browse and search for all HEAL-funded studies as well as other HEAL-relevant datasets. Findings from this work will be disseminated through publications and presentations at national and international professional conferences.

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

SELECT AGENTS/ BIOHAZARDOUS MATERIALS

NO select agents are used in this research.

Multiple PD/PI Leadership Plan

For this project we have assembled a team of three investigators who offer complementary areas of expertise that are critical to the success of the proposed study. This collaborative proposal has been conceived and written through the close cooperation of the *contact* principal investigator (PI); **Dr. Chani Traube** (Weill Cornell Medicine) and her colleagues; **Dr. Michael Bell** (Children's National Medical Center) and **Dr. Richard Holubkov** (University of Utah Health). We feel that this multiple PI arrangement is most suitable for our purposes, harnessing; 1) Dr. Holubkov's expertise as senior biostatistician and Co-Principal Investigator of the NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN) Data Coordinating Center (DCC); 2) Dr. Bell's expertise in pediatric neurocritical care and management of large, multi-site pediatric clinical trials, and, 3) Dr. Traube's clinical expertise in pediatrics, pediatric critical illness, delirium, and pediatric ICU (PICU) outcomes as well as expertise in designing and operationalizing pediatric research in the complex PICU environment.

Contact PI and Administrative Responsibilities

Dr. Traube will serve as contact PI and will provide oversight for the entire project and development and implementation of all policies, procedures and processes. Dr. Traube will oversee the clinical sites with respect to data collection and will assume fiscal and administrative management duties. Additionally, Dr. Traube will be responsible for the implementation of the scientific agenda, the leadership plan and the specific aims and ensure that systems are in place to guarantee institutional compliance with US Laws, DHHS, and NIH policies including biosafety, human and animal research, data and facilities and will be responsible for all communication with NIH and submission of annual reports.

Scientific Oversight

Drs. Traube, Holubkov, and Bell will share responsibility for directing the proposed research activities. Overall, Dr. Traube will have primary responsibility for all activities related to this proposal and will be responsible for standardization of operating procedures across the clinical sites and overall management of the study. Dr. Traube's Program Manager will work under her direction to ensure regulatory compliance, scientific milestones, and data analysis is performed in a timely manner.

Dr. Holubkov will have primary responsibility for activities related to the Data Coordinating Center (DCC) as well as preparing the single IRB protocol, obtaining IRB approvals at recruitment sites, and will oversee analysis of the qualitative data collected in this study.

Dr. Bell will have primary responsibility for coordinating clinical site activities related to the enrollment of subjects at CPCCRN sites and central pharmacy.

Communications

Drs. Traube, Holubkov, and Bell will execute central sIRB procedures and develop an operation manual. They will maintain communication through monthly meetings to approve final protocols, supervise overall execution of the study, generate and approve study policies, consider modifications of the protocol and operations, and draft study-related publications, as well as the redirection of funds, if necessary. Dr. Traube will meet with grant/program management weekly and provide monthly team updates and reports. A quarterly meeting will be held with all of the site-investigators.

The Steering Committee will serve as the main decision-making body for the project. Members of the Steering Committee will consist of Drs. Traube, Bell, And Holubkov as well a representative from the NICHD HEAL-KIDS, a parent advocate, medical monitor and Co-investigators. The Steering Committee will meet monthly via conference call and approve the final protocols, supervise overall execution of the study, generate and approve study policies, consider modifications of the protocol and operations, and plan and draft study-related publications. Each full member will have one vote. Dr. Traube will be responsible for implementing policies approved by the Steering Committee.

Publications and Intellectual Property

Drs. Traube, Holubkov, and Bell will develop a Publication Policy to ensure authorship for all site PIs and co-investigators in the study and that any intellectual property developed by these investigators during the course of the project is protected according to institutional policies. Dr. Traube will be responsible for implementing the policies approved in accordance to the HEAL Public Access and Data Sharing Policy.

Conflict Resolution

If a potential conflict develops, Drs. Traube, Holubkov, and Bell shall meet and attempt to resolve the dispute. If they fail to resolve the dispute, the disagreement shall be referred to a 3-person arbitration committee consisting of an impartial senior faculty member from each institution mutually agreed upon by all PIs. No members of the arbitration committee will be directly involved in the research grant or disagreement.

Change in PI Location

In the case that one of the PIs moves to a new institution, Drs. Traube, Holubkov, and Bell will continue to act as multi-PIs for this proposed grant. If a PI moves to a new institution, attempts will be made to transfer the relevant portion of the grant to the new institution.

BIBLIOGRAPHY & REFERENCES - OPTICOM

1. Yaster M, Deshpande JK. Management of pediatric pain with opioid analgesics. *J Pediatr.* 1988 Sep;113(3):421–9.
2. Owens ME. Pain in infancy: conceptual and methodological issues. *Pain.* 1984 Nov;20(3):213–30.
3. Anand KJ, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet Lond Engl.* 1987 Jan 31;1(8527):243–8.
4. Kelley-Quon LI, Kirkpatrick MG, Ricca RL, Baird R, Harbaugh CM, Brady A, et al. Guidelines for Opioid Prescribing in Children and Adolescents After Surgery: An Expert Panel Opinion. *JAMA Surg.* 2021 Jan 1;156(1):76–90.
5. Tobias JD. Acute Pain Management in Infants and Children—Part 2: Intravenous Opioids, Intravenous Nonsteroidal Anti-Inflammatory Drugs, and Managing Adverse Effects. *Pediatr Ann.* 2014 Jul 1;43(7):e169–75.
6. Smith HAB, Besunder JB, Betters KA, Johnson PN, Srinivasan V, Stormorken A, et al. 2022 Society of Critical Care Medicine Clinical Practice Guidelines on Prevention and Management of Pain, Agitation, Neuromuscular Blockade, and Delirium in Critically Ill Pediatric Patients With Consideration of the ICU Environment and Early Mobility. *Pediatr Crit Care Med.* 2022 Feb;23(2):e74–110.
7. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al. Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit. *Crit Care Med.* 2013 Jan;41(1):278–80.
8. Sigakis MJG, Bittner EA. Ten Myths and Misconceptions Regarding Pain Management in the ICU: Crit Care Med. 2015 Nov;43(11):2468–78.
9. Villarosa L. How False Beliefs in Physical Racial Difference Still Live in Medicine Today. *The New York Times [Internet].* 2019 Aug 14 [cited 2023 Oct 11]
10. Anderson KO, Green CR, Payne R. Racial and ethnic disparities in pain: causes and consequences of unequal care. *J Pain.* 2009 Dec;10(12):1187–204.
11. Drogell K, Kincade B, Melaku M, Mangira C, Burns A, Krizo J. Race and Sex Are Associated With Variations in Pain Management in Patients Presenting to the Emergency Department With Undifferentiated Abdominal Pain. *J Emerg Med.* 2022 Nov;63(5):629–35.
12. Kaseweter KA, Drwecki BB, Prkachin KM. Racial differences in pain treatment and empathy in a Canadian sample. *Pain Res Manag.* 2012;17(6):381–4.
13. Sabin JA, Greenwald AG. The influence of implicit bias on treatment recommendations for 4 common pediatric conditions: pain, urinary tract infection, attention deficit hyperactivity disorder, and asthma. *Am J Public Health.* 2012 May;102(5):988–95.
14. Johnson TJ, Winger DG, Hickey RW, Switzer GE, Miller E, Nguyen MB, et al. A comparison of physician implicit racial bias towards adults versus children. *Acad Pediatr.* 2017 Mar;17(2):120–6.
15. Puumala SE, Burgess KM, Kharbanda AB, Zook HG, Castille DM, Pickner WJ, et al. The Role of Bias by Emergency Department Providers in Care for American Indian Children. *Med Care.* 2016 Jun;54(6):562–9.
16. Paquette E, Shukla A, Smith T, Prendergast T, Duyar S, Rychlik K, et al. Barriers to Enrollment in a Pediatric Critical Care Biorepository. *Pediatr Res.* 2023 Aug;94(2):803–10.

17. Sholle ET, Pinheiro LC, Adekkanattu P, Davila MA, Johnson SB, Pathak J, et al. Underserved populations with missing race ethnicity data differ significantly from those with structured race/ethnicity documentation. *J Am Med Inform Assoc.* 2019 Aug 1;26(8–9):722–9.
18. Brewster RCL, Steinberg JR, Magnani CJ, Jackson J, Wong BO, Valikodath N, et al. Race and Ethnicity Reporting and Representation in Pediatric Clinical Trials. *Pediatrics.* 2023 Apr 1;151(4):e2022058552.
19. Najjar N, Opolka C, Fitzpatrick AM, Grunwell JR. Geospatial Analysis of Social Determinants of Health Identifies Neighborhood Hot Spots Associated With Pediatric Intensive Care Use for Acute Respiratory Failure Requiring Mechanical Ventilation. *Pediatr Crit Care Med.* :10.1097/PCC.0000000000002986.
20. Hong L, Page SE. Groups of diverse problem solvers can outperform groups of high-ability problem solvers. *Proc Natl Acad Sci.* 2004 Nov 16;101(46):16385–9.
21. Drwecki BB, Moore CF, Ward SE, Prkachin KM. Reducing racial disparities in pain treatment: the role of empathy and perspective-taking. *Pain.* 2011 May;152(5):1001–6.
22. Sukhera J, Watling C. A Framework for Integrating Implicit Bias Recognition Into Health Professions Education. *Acad Med.* 2018 Jan;93(1):35–40.
23. Watson RS, Beers SR, Asaro LA, Burns C, Koh MJ, Perry MA, et al. Association of Acute Respiratory Failure in Early Childhood With Long-term Neurocognitive Outcomes. *JAMA.* 2022 Mar 1;327(9):836.
24. Baarslag MA, Jhingoer S, Ista E, Allegaert K, Tibboel D, van Dijk M. How often do we perform painful and stressful procedures in the paediatric intensive care unit? A prospective observational study. *Aust Crit Care Off J Confed Aust Crit Care Nurses.* 2019 Jan;32(1):4–10.
25. Düzkaya DS, Kuğuoğlu S. Assessment of Pain During Endotracheal Suction In the Pediatric Intensive Care Unit. *Pain Manag Nurs.* 2015 Feb 1;16(1):11–9.
26. Kortesluoma RL, Nikkinen M, Serlo W. “You Just Have to Make the Pain Go Away”—Children’s Experiences of Pain Management. *Pain Manag Nurs.* 2008 Dec 1;9(4):143–149.e5.
27. Patel AK, Trujillo-Rivera E, Faruqe F, Heneghan JA, Workman TE, Zeng-Treitler Q, et al. Sedation, Analgesia, and Neuromuscular Blockade: An Assessment of Practices From 2009 to 2016 in a National Sample of 66,443 Pediatric Patients Cared for in the ICU. *Pediatr Crit Care Med.* 2020 Sep;21(9):e599–609.
28. Curley MAQ, Wypij D, Watson RS, Grant MJC, Asaro LA, Cheifetz IM, et al. Protocolized Sedation vs Usual Care in Pediatric Patients Mechanically Ventilated for Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA.* 2015 Jan 27;313(4):379.
29. Chung CP, Callahan ST, Cooper WO, Dupont WD, Murray KT, Franklin AD, et al. Outpatient Opioid Prescriptions for Children and Opioid-Related Adverse Events. *Pediatrics.* 2018 Aug 1;142(2):e20172156.
30. Krane EJ, Weisman SJ, Walco GA. The National Opioid Epidemic and the Risk of Outpatient Opioids in Children. *Pediatrics.* 2018 Aug 1;142(2):e20181623.
31. Berde C, Nurko S. Opioid Side Effects — Mechanism-Based Therapy. *N Engl J Med.* 2008 May 29;358(22):2400–2.
32. Grunkemeier DMS, Cassara JE, Dalton CB, Grossman DA. The Narcotic Bowel Syndrome: Clinical Features, Pathophysiology, and Management. *Clin Gastroenterol Hepatol.* 2007 Oct;5(10):1126–39.
33. Okie S. A Flood of Opioids, a Rising Tide of Deaths. *N Engl J Med.* 2010 Nov 18;363(21):1981–5.

34. Maxwell JC. The prescription drug epidemic in the United States: A perfect storm. *Drug Alcohol Rev.* 2011 May;30(3):264–70.
35. Lee M, Silverman S, Hansen H, Patel V, Manchikanti L. A Comprehensive Review of Opioid-Induced Hyperalgesia. *Pain Physician.*
36. Ista E, Traube C, De Neef M, Schieveld J, Knoester H, Molag M, et al. Factors Associated With Delirium in Children: A Systematic Review and Meta-Analysis. *Pediatr Crit Care Med.* 2023 May;24(5):372–81.
37. Traube C, Silver G, Gerber LM, Kaur S, Mauer EA, Kerson A, et al. Delirium and Mortality in Critically Ill Children: Epidemiology and Outcomes of Pediatric Delirium. *Crit Care Med.* 2017 May;45(5):891–8.
38. Galinkin J, Koh JL, COMMITTEE ON DRUGS, SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE. Recognition and Management of Iatrogenically Induced Opioid Dependence and Withdrawal in Children. *PEDIATRICS.* 2014 Jan 1;133(1):152–5.
39. Martyn JAJ, Mao J, Bittner EA. Opioid Tolerance in Critical Illness. Ingelfinger JR, editor. *N Engl J Med.* 2019 Jan 24;380(4):365–78.
40. Geneslaw AS, Lu Y, Miles CH, Hua M, Cappell J, Smerling AJ, et al. Long-Term Increases in Mental Disorder Diagnoses After Invasive Mechanical Ventilation for Severe Childhood Respiratory Disease: A Propensity Matched Observational Cohort Study. *Pediatr Crit Care Med.* 2021 Dec;22(12):1013–25.
41. Wren A, Ross A, D'Souza G, Almgren C, Feinstein A, Marshall A, et al. Multidisciplinary Pain Management for Pediatric Patients with Acute and Chronic Pain: A Foundational Treatment Approach When Prescribing Opioids. *Children.* 2019 Feb 21;6(2):33.
42. Dash GF, Wilson AC, Morasco BJ, Feldstein Ewing SW. A Model of the Intersection of Pain and Opioid Misuse in Children and Adolescents. *Clin Psychol Sci.* 2018 Sep;6(5):629–46.
43. Anand K, Hall RW, Desai N, Shephard B, Bergqvist LL, Young TE, et al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *The Lancet.* 2004 May;363(9422):1673–82.
44. Szatkowski L, Sharkey D, Budge H, Ojha S. Association between opioid use during mechanical ventilation in preterm infants and evidence of brain injury: a propensity score-matched cohort study. *eClinicalMedicine.* 2023 Nov;65:102296.
45. Subramaniam B, Shankar P, Shaefi S, Mueller A, O'Gara B, Banner-Goodspeed V, et al. Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial. *JAMA.* 2019 Feb 19;321(7):686.
46. Barnes-Daly MA, Phillips G, Ely EW. Improving Hospital Survival and Reducing Brain Dysfunction at Seven California Community Hospitals: Implementing PAD Guidelines Via the ABCDEF Bundle in 6,064 Patients. *Crit Care Med.* 2017 Feb;45(2):171–8.
47. Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, et al. Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. *Crit Care Med.* 2019 Jan;47(1):3–14.
48. Mallet C, Desmeules J, Pegahy R, Eschalier A. An Updated Review on the Metabolite (AM404)-Mediated Central Mechanism of Action of Paracetamol (Acetaminophen): Experimental Evidence and Potential Clinical Impact. *J Pain Res.* 2023 Mar;Volume 16:1081–94.

49. Zuppa AF, Hammer GB, Barrett JS, Kenney BF, Kassir N, Mouksassi S, et al. Safety and Population Pharmacokinetic Analysis of Intravenous Acetaminophen in Neonates, Infants, Children, and Adolescents With Pain or Fever. *J Pediatr Pharmacol Ther.* 2011 Oct 1;16(4):246–61.
50. Anderson BJ, Pons G, Autret-Leca E, Allegaert K, Boccard E. Pediatric intravenous paracetamol (propacetamol) pharmacokinetics: a population analysis1. *Pediatr Anesth.* 2005;15(4):282–92.
51. Palmer GM, Atkins M, Anderson BJ, Smith KR, Culnane TJ, McNally CM, et al. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth.* 2008 Oct;101(4):523–30.
52. Patel AK, Gai J, Trujillo-Rivera E, Faruqe F, Kim D, Bost JE, et al. National Intravenous Acetaminophen Use in Pediatric Inpatients From 2011–2016. *J Pediatr Pharmacol Ther JPPT.* 2022;27(4):358–65.
53. Chidambaran V, Subramanyam R, Ding L, Sadhasivam S, Geisler K, Stubbeman B, et al. Cost-effectiveness of intravenous acetaminophen and ketorolac in adolescents undergoing idiopathic scoliosis surgery. *Pediatr Anesth.* 2018 Mar;28(3):237–48.
54. Olbrecht VA, Ding L, Spruance K, Hossain M, Sadhasivam S, Chidambaran V. Intravenous Acetaminophen Reduces Length of Stay Via Mediation of Postoperative Opioid Consumption After Posterior Spinal Fusion in a Pediatric Cohort. *Clin J Pain.* 2018 Jul;34(7):593.
55. Litvak KM, McEvoy GK. Ketorolac, an injectable nonnarcotic analgesic. *Clin Pharm.* 1990 Dec;9(12):921–35.
56. National Center for Biotechnology Information. PubChem Compound Summary for CID 3826, Ketorolac. Accessed Nov. 16, 2023.54. Cepeda MS, Silva C. Comparison of Morphine, Ketorolac, and Their Combination for Postoperative Pain. *2005;103(6).*
57. Cepeda MS, Silva C. Comparison of Morphine, Ketorolac, and Their Combination for Postoperative Pain. *2005;103(6).*
58. Chen JY, Ko TL, Wen YR, Wu SC, Chou YH, Yien HW, et al. Opioid-sparing effects of ketorolac and its correlation with the recovery of postoperative bowel function in colorectal surgery patients: a prospective randomized double-blinded study. *Clin J Pain.* 2009;25(6):485–9.
59. Gillies GWA, Kenny GNC, Bullingham RES, McARDLE CS. The morphine sparing effect of ketorolac tromethamine. *Anaesthesia.* 1987;42(7):727–31.
60. Gupta A, Daggett C, Drant S, Rivero N, Lewis A. Prospective randomized trial of ketorolac after congenital heart surgery. *J Cardiothorac Vasc Anesth.* 2004 Aug;18(4):454–7.
61. Papacci P, de Francisci G, Iacobucci T, Giannantonio C, De Carolis MP, Zecca E, et al. Use of intravenous ketorolac in the neonate and premature babies. *Pediatr Anesth.* 2004;14(6):487–92.
62. Moffett BS, Wann TI, Carberry KE, Mott AR. Safety of ketorolac in neonates and infants after cardiac surgery. *Paediatr Anaesth.* 2006 Apr;16(4):424–8.
63. Dawkins TN, Barclay CA, Gardiner RL, Krawczeski CD. Safety of intravenous use of ketorolac in infants following cardiothoracic surgery. *Cardiol Young.* 2009 Feb;19(1):105–8.
64. Lieh-Lai MW, Kauffman RE, Uy HG, Danjin M, Simpson PM. A randomized comparison of ketorolac tromethamine and morphine for postoperative analgesia in critically ill children. *Crit Care Med.* 1999 Dec;27(12):2786–91.
65. Lucas SS, Nasr VG, Ng AJ, Joe C, Bond M, DiNardo JA. Pediatric Cardiac Intensive Care Society 2014 Consensus Statement: Pharmacotherapies in Cardiac Critical Care: Sedation, Analgesia and Muscle Relaxant. *Pediatr Crit Care Med.* 2016;17(3 Suppl 1):S3-S15. doi:10.1097/PCC.0000000000000619

66. Hamel LM, Penner LA, Albrecht TL, et al: Barriers to Clinical Trial Enrollment in Racial and Ethnic Minority Patients With Cancer. *Cancer Control* 23:327-337, 2016.
67. Hughson JA, Woodward-Kron R, Parker A, et al: A review of approaches to improve participation of culturally and linguistically diverse populations in clinical trials. *Trials* 17:263, 2016.
68. Yeager KA, Bauer-Wu S: Cultural humility: essential foundation for clinical researchers. *Appl Nurs Res* 26:251-6, 2013.
69. Smedley, B. D., Stith, A. Y., & Nelson, A. R. (Eds.). (2003). *Unequal treatment: Confronting racial and ethnic disparities in health care*. The National Academies Press.
70. Dickason R, Chauhan V, Mor A, Ibler E, Kuehnle S, Mahoney D, et al. Racial Differences in Opiate Administration for Pain Relief at an Academic Emergency Department. *West J Emerg Med*. 2015 May 1;16(3):372–80.
71. Flores G, Abreu M, Schwartz I, Hill M. The importance of language and culture in pediatric care: case studies from the Latino community. *J Pediatr*. 2000 Dec;137(6):842–8.
72. Rosenbloom JM, Mekonnen J, Tron LE, Alvarez K, Alegria M. Racial and Ethnic Health Services Disparities in Pediatric Anesthesia Practice: A Scoping Review. *J Racial Ethn Health Disparities*. 2021 Apr;8(2):384–93.
73. Sborov KD, Haruno LS, Raszka S, Poon SC. Racial and Ethnic Disparities in Pediatric Musculoskeletal Care. *Curr Rev Musculoskelet Med*. 2023 Aug 7;16(10):488–92.
74. Jimenez N, Seidel K, Martin LD, Rivara FP, Lynn AM. Perioperative Analgesic Treatment in Latino and non-Latino Pediatric Patients. *J Health Care Poor Underserved*. 2010 Feb;21(1):229–36.
75. Natale JE, Asaro LA, Joseph JG, Ulysse C, Ascenzi J, Bowens C, et al. Association of Race and Ethnicity with Sedation Management in Pediatric Intensive Care. *Ann Am Thorac Soc*. 2021 Jan;18(1):93–102.
76. Chapman EN, Kaatz A, Carnes M. Physicians and Implicit Bias: How Doctors May Unwittingly Perpetuate Health Care Disparities. *J Gen Intern Med*. 2013 Nov;28(11):1504–10.
77. Hall WJ, Chapman MV, Lee KM, Merino YM, Thomas TW, Payne BK, et al. Implicit Racial/Ethnic Bias Among Health Care Professionals and Its Influence on Health Care Outcomes: A Systematic Review. *Am J Public Health*. 2015 Dec;105(12):e60–76.
78. Stone J, Moskowitz GB. Non-conscious bias in medical decision making: what can be done to reduce it? *Med Educ*. 2011;45(8):768–76.
79. Andrist E, Riley CL, Brokamp C, Taylor S, Beck AF. Neighborhood Poverty and Pediatric Intensive Care Use. *Pediatrics*. 2019 Dec;144(6):e20190748.
80. Brown LE, França UL, McManus ML. Socioeconomic Disadvantage and Distance to Pediatric Critical Care. *Pediatr Crit Care Med*. 2021 Dec;22(12):1033–41.
81. Mitchell C, Hobcraft J, McLanahan SS, Siegel SR, Berg A, Brooks-Gunn J, et al. Social disadvantage, genetic sensitivity, and children's telomere length. *Proc Natl Acad Sci*. 2014 Apr 22;111(16):5944–9.
82. Epstein D, Reibel M, Unger JB, Cockburn M, Escobedo LA, Kale DC, et al. The Effect of Neighborhood and Individual Characteristics on Pediatric Critical Illness. *J Community Health*. 2014 Aug;39(4):753–9.
83. Slain KN, Wurtz MA, Rose JA. US children of minority race are less likely to be admitted to the pediatric intensive care unit after traumatic injury, a retrospective analysis of a single pediatric trauma center. *Inj Epidemiol*. 2021 Apr 12;8:14.

84. Porter A, Brown CC, Tilford JM, Thomas K, Maxson RT, Sexton K, et al. Association of Insurance Status With Treatment and Outcomes in Pediatric Patients With Severe Traumatic Brain Injury. *Crit Care Med.* 2020 Jul;48(7):e584.
85. Paquette ET. Reckoning with Redlining and Other Structural Barriers to Health of Critically Ill Children: Addressing systemic racism will require shifting the focus from micro- to macro- level analysis of social risks. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc.* 2022 Aug 1;23(8):662–5.
86. Grunwell JR, Opolka C, Mason C, Fitzpatrick AM. Geospatial Analysis of Social Determinants of Health Identifies Neighborhood Hot Spots Associated with Pediatric Intensive Care Use for Life-threatening Asthma. *J Allergy Clin Immunol Pract.* 2022 Apr;10(4):981-991.e1.
87. Agency for Toxic Substances and Disease Registry. CDC Social Vulnerability Index. A Tool to Identify Socially Vulnerable Communities. Fact Sheet. Last accessed 24 Oct 2023.
88. Paquette E, Shukla A, Davidson J, Rychlik K, Davis M. Burden or Opportunity? *Ethics Hum Res.* 2019 May;41(3):2–12.
89. Taylor HA, Porter KM, Paquette ET, McCormick JB, Tumilty E, Arnold JF, et al. Creating a Research Ethics Consultation Service: Issues to Consider. *Ethics Hum Res.* 2021 Sep;43(5):18–25.
90. Zurca AD, Suttle ML, October TW. An Antiracism Approach to Conducting, Reporting, and Evaluating Pediatric Critical Care Research. *Pediatr Crit Care Med.* 2022 Feb;23(2):129–32.
91. Palmer RC, Ismond D, Rodriguez EJ, Kaufman JS. Social Determinants of Health: Future Directions for Health Disparities Research. *Am J Public Health.* 2019 Jan;109(Suppl 1):S70–1.
92. Manworren RCB, Hynan LS. Clinical validation of FLACC: preverbal patient pain scale. *Pediatr Nurs.* 2003;29(2):140–6.
93. Voepel-Lewis T, Zanotti J, Dammeyer JA, Merkel S. Reliability and Validity of the Face, Legs, Activity, Cry, Consolability Behavioral Tool in Assessing Acute Pain in Critically Ill Patients. *Am J Crit Care.* 2010 Jan 1;19(1):55–61.
94. Khemani RG, Hotz J, Morzov R, Flink R, Kamerkar A, Ross PA, et al. Evaluating Risk Factors for Pediatric Post-extubation Upper Airway Obstruction Using a Physiology-based Tool. *Am J Respir Crit Care Med.* 2016 Jan 15;193(2):198–209.
95. Dorfman TL, Sumamo Schellenberg E, Rempel GR, Scott SD, Hartling L. An evaluation of instruments for scoring physiological and behavioral cues of pain, non-pain related distress, and adequacy of analgesia and sedation in pediatric mechanically ventilated patients: A systematic review. *Int J Nurs Stud.* 2014 Apr;51(4):654–76.
96. Wandner LD, Domenichiello AF, Beierlein J, Pogorzala L, Aquino G, Siddons A, Porter L, Atkinson J; NIH Pain Consortium Institute and Center Representatives. NIH's Helping to End Addiction Long-term® Initiative (NIH HEAL Initiative) Clinical Pain Management Common Data Element Program. *J Pain.* 2021 Sep 9:S1526-5900(21)00321-7. doi: 10.1016/j.jpain.2021.08.005. Epub ahead of print. PMID: 34508905.
97. Kent DM, Paulus JK, van Klaveren D, D'Agostino R, Goodman S, Hayward R, Ioannidis JPA, Patrick-Lake B, Morton S, Pencina M, Raman G, Ross JS, Selker HP, Varadhan R, Vickers A, Wong JB, Steyerberg EW. The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement. *Ann Intern Med.* 2020 Jan 7;172(1):35-45. doi: 10.7326/M18-3667. Epub 2019 Nov 12. PMID: 31711134; PMCID: PMC7531587.

CONSORTIUM/CONTRACTUAL AGREEMENTS – OPTICOM

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy. Applicable statements of intent to enter into consortium agreements have been obtained by the research team and will remain on file with the Department and OSRA WCMC. These include the following:

University of Utah, Salt Lake City, UT

Dr. Richard Holubkov will participate as MPI and DCC Lead through a subcontract from Weill Cornell Medicine (WCM) to the University of Utah. Dr. Holubkov will be responsible for all aspects of the proposed Data Coordinating Center (DCC) activities, including ensuring that appropriate data are collected to accomplish the goals of the study. Dr. Holubkov will oversee development of analysis datasets, provide statistical expertise for the project and present interim analyses at DSMB meetings. **Dr. Ron Reeder** will serve as the primary statistical contact and will direct the efforts of the DCC to provide data management and statistical support for the proposed study.

Children's Research Institute, Washington, DC

Dr. Michael Bell will participate as MPI through a subcontract from WCM to Children's Research Institute. Dr. Bell will be responsible to report information to NIH/FDA related to study activities, participate in Executive Committee and Steering Committee activities to ensure the progress of the project and be responsible for writing and dissemination of findings among other activities. Coinvestigator, **Dr. Vanessa Madrigal** will participate as an active member of the Steering Committee to ensure ethical conduct of the trial and assist with any troubleshooting that may arise regarding challenges related to patient recruitment or concerns of the stakeholders of the study.

Johns Hopkins University (JHU), Baltimore, MD

Dr. Sapna Kudchadkar will participate as coinvestigator through a subcontract form WCM to JHU and will advise in all phases of the proposed research, including study design, implementation and review of the data analysis and interpretation.

Ann & Robert H. Lurie Children's Hospital of Chicago, IL

Dr. Erin Paquette will participate as coinvestigator through a subcontract form WCM to Lurie Children's and will assist the team in establishing study procedures from the outset that will minimize the chance for inadequate pain assessment and management, through educating study coordinators about the potential for bias to influence study recruitment. She will also provide education to study participants regarding the concept of randomization to minimize the effect of randomization as a barrier.

These investigators will provide critical scientific expertise, knowledge, skills, and services to the proposed U01 Project, **OPTICOM**, and are thus critical participants through subcontracts to Weill Cornell Medicine. Weill Cornell Medicine (WCM) is the applicant organization and will provide administrative oversight and management under Dr. Chani Traube (contact PI) in collaboration with MPIs, Dr. Michael Bell and Dr. Richard Holubkov.

Consortium Agreements will be established in accordance with institutional and federal regulations through central administrative offices for the corresponding institutions and will be executed by organizational representatives with appropriate level of authority.

LETTERS OF SUPPORT

Please find the following letters of support for the **OPTICOM** Project are in the pages that follow. These include:

Institutional Letters of Support

Name	Title	Support
Michael Dean, MD, MBA	Collaborative Pediatric Critical Care Research Network (CPCCRN) Steering Committee; DCC Principal Investigator	CPCCRN Network Infrastructure support
Deborah L. Amey	Advisory Board Member, Family Network Collaborative	CPCCRN Family Network Collaborative support & participation
Aleta R. Gunsul, MPA	Executive Director, Office of Sponsored Research Administration, Weill Cornell Medicine	Grants and contracts management support
Sallie Permar, MD, PhD	Chair, Department of Pediatrics, Weill Cornell Medicine	Department Program, clinical, and administrative support
Julianne Imperato-McGinley, MD	Director, Weill Cornell Medicine Clinical and Translational Science Center (CTSC)	CTSC clinical support
Rachel Hess, MD, MS & Jennifer Juhl Majersik, MD, MS, FAHA ,FAAN	Co-Directors, Utah Clinical & Translational Science Institute (CTSI)	CTSI clinical support
Margaret Parker, MD, MCCM	Professor Emerita of Pediatrics. Stony Brook University	Consultant, Medical Monitor

Participating Clinical Sites Letters of Commitment

Letters of commitment from 14 clinical sites participating in **OPTICOM** are in the pages that follow. **OPTICOM** investigators are dedicated to the development of the next generation of physician scientists and junior faculty participating are also listed below.

Clinical Site	Investigator	Junior Faculty
Arkansas Children's Hospital	Ron C. Sanders, Jr, MD, MS, FAAP, FCCM	
Children's National Medical Center	Michael Bell, MD	Nada Mallick, MD and Elizabeth Elliott, MD
Children's Hospital of Michigan	Kathleen Meert, MD	Tageldin Ahmed, MD
CHOC - Children's Hospital of Orange County	Adam J. Schwarz, MD	
CHOP - Children's Hospital of Philadelphia	Robert A. Berg, MD, MCCM, FAAP, FAHA	Heather Wolfe, MD, MSHP
Christus Children's	Mohammad K. Salameh, MD	
MUSC - Medical University of South Carolina	John Costello, MD, MPH	Austin Biggs, MD
Nationwide Children's Hospital	Mark W. Hall, MD, FCCM	Ambrish B. Patel, MD
Texas Children' Hospital	Ayse Akcan-Arikan, MD	
University Hospitals Rainbow Babies & Children's	Steven L. Shein, MD	

Clinical Site	Investigator	Junior Faculty
University of California, Davis Health	Moonjoo Han, MD	
University of Pittsburgh	Joseph Carcillo, MD	To be assigned
University of Utah Health	Jill Sweney, MD, MBA	
VCU - Virginia Commonwealth University	Nikki Miller Ferguson, MD	



J. Michael Dean MD, M.B.A.
Professor and Vice Chairman for Research

Chani Traube, MD, FAAP, FCCM
Professor of Pediatrics
Weill Cornell Medicine

Michael Bell, MD (MPI)
Division Chief, Critical Care Medicine
Children's National Medical Center

Richard Holubkov, PhD (MPI)
Professor, Department of Pediatrics
University of Utah School of Medicine

Dear Chani, Michael, and Rich,

As the original PI of the PL1HD105462 grant currently funding the *Eunice Kennedy Shriver NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN)*, I am writing to indicate the strong support of the network for your novel proposal: Optimizing Pain Treatment in Children on Mechanical Ventilation: the OPTICOM Study. Normally the Chair of the CPCCRN Steering Committee writes letters of support from CPCCRN, but since you (Chani) are the Chair, the network considered it appropriate for me to write this letter on its behalf since I am independent of your grant proposal.

I have been the PI for the DCC of CPCCRN since its inception nearly 20 years ago, and the network has a well established mechanism for conceiving, developing, implementing, and completing multi-institutional trials in the complex Pediatric Intensive Care Unit (PICU) environment. Our scientific process includes proposing concepts to the Steering Committee, and then developing the very best concepts into protocols and grant proposals. The OPTICOM Study began as such a concept, and was thoroughly developed in a collaborative manner with the CPCCRN Steering Committee, and perhaps as importantly, with the CPCCRN Family Network Collaborative (FNC). Input from the FNC was important for defining the primary outcome of the OPTICOM Study, as parents indicated that the single-most distressing aspect of mechanical ventilation for acute respiratory failure is acute episodic pain. There is a strong scientific premise to the current proposal that routine non-opioid analgesics can reduce these acute episodes when used to supplement opioid administration, and in fact, may reduce delirium and reduce the length of mechanical ventilation. We (the Steering Committee) have made intellectual contributions during development of the protocol, and our support is enthusiastic and unanimous. This proposal is uniquely appropriate for the HEAL KIDS Initiative Clinical Trials Program, and we are delighted that this funding opportunity is available to fund OPTICOM. Since CPCCRN has a well established infrastructure, the trial will be rapidly initiated and completed, contributing to success for the HEAL KIDS program. We wish you the best of success with your grant submission and look forward to conducting the trial.

Sincerely yours,

A handwritten signature in black ink that reads "J. Michael Dean, M.D., M.B.A."

J. Michael Dean, M.D., M.B.A.
On behalf of the CPCCRN Steering Committee

Pediatric Critical Care

PO Box 581289; 295 Chipeta Way
Salt Lake City, UT 84158
801-581-5271

October 30, 2023

October 27, 2023

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

I am delighted to serve as a member of the Advisory Board for this grant application, “Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)”. I am a leading member of the Family Network Collaborative (FNC) at CPCCRN (the Collaborative Pediatric Critical Care Research Network). Our group is composed of 13 family members of children who have experienced critical illness.

We are grateful that the OPTICOM study team is deeply committed to incorporating our unique and informed viewpoints in every aspect of study design. We met with you to discuss our children’s experiences while on invasive mechanical ventilation, and shared our perspective that *the single most distressing aspect of acute respiratory failure is episodic pain*. We reviewed preliminary data, and together we discussed the optimal strategy for a clinical trial designed to reduce pain.

The members of the FNC are deeply supportive of the OPTICOM trial and pledge to remain engaged throughout the process, in order to maintain focus on family perspectives, expand enrollment of a diverse patient population, and maximize the impact of the research findings. Our perspectives as parents and stakeholders will add greatly to the rigor of the study, and I thank you for including us as advisors on this project from the start.

I strongly believe that OPTICOM has the potential to improve outcomes in families after critical illness. The FNC will remain engaged over the five years of the study, and we are committed to do everything possible to ensure its successful completion.

Please do not hesitate to reach out to me with any questions.

Sincerely,

Deborah L. Amey

Electronically signed
by: Deborah L. Amey
Date: Oct 27, 2023
12:34 PDT


Oct 27, 2023



Weill Cornell Medicine

Office of Sponsored Research Administration

1300 York Avenue, Box 89
New York, NY 10065-4805
646-962-8290
grantsandcontracts@med.cornell.edu

October 16, 2023

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

It is with great enthusiasm that I offer my support for the HEAL Initiative Clinical Trials Program, "Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)," in response to RFA-HD-24-011. OPTICOM aims to advance the treatment of acute pain in a diverse population of children across the age-spectrum. The program also aims to develop comprehensive evidence-based clinical guidelines for the management of pain in children with acute respiratory failure.

Weill Cornell Medicine's (WCM) research operations infrastructure has the depth, expertise and demonstrated track-record of success to provide efficient and expeditious management of this highly complex program. WCM maintains a robust infrastructure that oversees pre- and post-award program management needs through its Department of Research Business Operations (RBO). RBO houses both Weill Cornell Medicine's central grants management and contracting offices as well as a suite of dedicated, program specific, portfolio managers. RBO's offering is an innovative management structure unique to WCM's brand.

Weill Cornell Medicine's Research Business Operations (RBO) team will appoint dedicated personnel to support the administrative and financial management of OPTICOM. RBO has a combined expertise of many decades of experience and the deep knowledge required to provide comprehensive services in subcontracting, data sharing and management, and material transfer agreements, amongst project collaborators. RBO has the experience and infrastructure needed to rapidly initiate and manage contracts under the program.

RBO's integrated model of direct program support, combined with our central research management, comprises a force of over 50 research administration professionals at the ready. RBO's comprehensive and overarching approach to research management services is our unique, quintessential model for facilitating all aspects of the program's objectives needed to make this project a success.

We have an established track record of success across the Weill Cornell research landscape and with the Department of Pediatrics specifically, supporting multicomponent NIH funded program projects in collaboration with their Program Management Team.

We enthusiastically offer our full support to this project.

Aleta R. Gunsul

Aleta Gunsul, MPA
Executive Director, Research Business Operations
Authorized Organizational Representative (AOR)
Weill Cornell Medicine



Sallie Permar, M.D., Ph.D.

Nancy C. Paduano Professor and Chair
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Pediatrician-in-Chief
New York-Presbyterian Komansky Children's Hospital
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November 1, 2023

Dear Chani and the members of the review team,

As Chair of the Department of Pediatrics, it is my pleasure and great honor to support this proposal **"Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)"** in response to RFA-HD-24-011. The proposal focuses on treatment optimization for pediatric patients, which is critically important at any time especially now as we deal with ongoing and new epidemics that affect this very sensitive population. Dr. Traube is a leading expert in the field, and there is no better candidate to lead this important collaborative work and bring that to the bedside in the most expedient manner.

Dr. Traube is an internationally recognized expert in Pediatric Delirium and Sedation Research and intensive care, the founding member of the Weill Cornell Delirium Work Group (DWG). She leads a multidisciplinary team of clinicians and researchers who spearhead research into delirium prevention and management in seriously ill children. Her work is federally funded by two important grants: R01 CA244500 and R01 HD099284. Both are collaborative projects that bring together excellent teams of experts and that produce remarkable results. She is also part of the #5 CA197730 (PI Prigerson), where she plays a vital part as key personnel working on develop EMPOWER and other studies addressing the emotional and social needs of children with cancer who are critically ill, as well as their parents. Dr. Traube has an impressive record of leading 25 delirium-related studies and she is the recipient of numerous awards and recognitions as a result of her work. Dr. Traube currently has 10 active approved IRBs at Weill Cornell Medicine and provides ongoing consultations to external institutions that are embarking on their delirium-related research projects.

Dr. Traube is also the Director of Clinical Research Mentoring in the Department of Pediatrics. In this role, Dr. Traube facilitates mentor-mentee relationships and supports the development of physician-scientists within the Department of Pediatrics. She offers extensive leadership skills, experience with multi-site clinical trials, support for the development of the next generation of physician-scientists, and a dedication to pediatric critical care. She has brought together a strong team of CPPCRN Network clinical sites, investigators, biostatisticians, and clinicians to ensure the success of the mentees in this very important program.

The Department of Pediatrics is fully prepared and well-positioned to support Dr. Traube and this new proposal that she has developed with her colleagues.

- We offer an excellent scientific environment as documented in the Facilities provided. This includes, but is not limited to a well-established NIH-funded Clinical Translational Science Center that leads clinical investigation support services and facilities and will provide an excellent resource to Dr. Traube and her team. This program offers substantial resources, services, and opportunities, and they closely collaborate with the clinical research coordinators in the Joined Clinical Trials Office and investigators at the Weill Cornell Medicine and other institutions in their large network.
- We also provide outstanding levels of administrative and clinical research support to our investigators. Dr. Traube is already working with the Joined Clinical Trials Office, which trains, oversees, and manages clinical research personnel and supports studies from their submission to the IRB, to their execution through recruitment and vigorous quality controls and data management expertise, to the completion and closeout.
- The administrative grant personnel support includes a truly outstanding team of pre-and-post award managers housed within the institutional Research Business Management group. They provide full support inclusive of application development and submission, but most importantly of careful financial planning and oversight that allows our investigators to always carry out their work in line with federal and

Contact PD/PI: Traube, Chani
institutional guidelines.

- Lastly, the Department of Pediatrics has a Program Management Team (PMT) that is poised to fully support Dr. Traube to ensure a smooth transition and efficient execution of regulatory and programmatic requirements, and administrative staff for coordination of required meetings. Our PMT has experience in efficiently executing multiple P01 Program Projects and U01 Clinical Studies (multi-sites) with budgets of >\$15M per year. They work seamlessly with the Research Business Management team and central grants office to ensure appropriate allocations and contract executions are complete.

Dr. Traube is a senior investigator with an excellent track record who has led multiple collaborative teams in her career. She is very well-positioned to take on this project as the contact PI. She has established an outstanding team of experts who will work together toward a common goal and who will change the clinical practice around the optimization of paid treatment in children. Weill Cornell Medicine is an excellent institution to house this project, and we offer many resources that will ensure the success of this work. I support this application without any reservation, and I urge you to consider this most seriously.

Regards,



Sallie Permar, MD, PhD
Chair, Department of Pediatrics
Weill Cornell Medicine



Weill Cornell Medicine

Clinical & Translational Science Center

A Weill Cornell Medical College Multi-Institutional Consortium with:

Weill Cornell Graduate School of Medical Sciences / NewYork-Presbyterian Hospital / Cornell University, Ithaca / Cornell University Cooperative Extension, New York City / Memorial Sloan Kettering Cancer Center / Hospital for Special Surgery / Hunter College School of Urban Public Health / Hunter College School of Nursing / Hunter Center for Translational and Basic Research (CTBR) / Animal Medical Center

1300 York Ave, Box 149, New York, NY 10065 • Tel: 646-962-8302 • Fax: 646-962-0534 • www.med.cornell.edu/ctsc

November 10, 2023

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

The Weill Cornell Clinical and Translational Science Center (CTSC) is a multi-institutional team endeavor to promote translational research and multidisciplinary collaboration with and across our partner institutions. As Associate Dean for Translational Research and Education and Director, I am delighted to support your proposal, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**" in response to RFA-HD-24-011 and pleased to offer the partnership of the CTSC at Weill Cornell to support this important program.

The mission of the CTSC is to provide an environment that allows optimal use of our considerable multi-institutional assets and the diversity of our patient population to translate discoveries at the bench to the bedside and to the community. The CTSC is a conduit through which essential resources, technological tools and education programs for all partners can be efficiently shared and managed.

We received the CTSA grant from the NIH in September 2007, the largest federal grant ever awarded to Weill Cornell Medicine, which was renewed in 2012 and most recently in 2017. The CTSC encompasses seven institutions under its collaborative umbrella and seeks to provide an environment that allows optimal use of our considerable multi-institutional assets and the diversity of our patient population to move translational research seamlessly from bench to bedside and to the community. The CTSC acts as a conduit through which essential resources, technological tools and education programs for all partners can be efficiently shared and managed.

Your proposal will benefit from the substantial resources, services and opportunities offered by our CTSC. The Research Design and Biostatistics Core (RDBC) is designed to support transinstitutional projects encompassing a broad spectrum of disciplines. Its principal objective is to provide biostatistical resources for the design and conduct of studies within the CTSC. Services Offered include 1) Study Design and Proposal Development 2) Implementation and Study Conduct 3) Data Management 4) Data Analysis 5) Presentation/Publication.

The Research Navigation Team (RNT) provides guidance and support to investigators by helping prepare protocol applications, providing information about CTSC resources, regulatory and administrative issues, and referring investigators to appropriate CTSC staff for consultation.

The Trial Innovation Center within the CTSC program assists investigator in conducting clinical trials better, faster, and more cost-efficiently. The TIC is charged with centralizing multi-site trial management across all the CTSC partner institutions thereby providing a robust, standardized and accessible infrastructure to facilitate rapid clinical trial implementation.

The CTSC also serves as the focus of investigator-initiated clinical and translational research at Weill Cornell, and an important part of our mission is to serve as a training facility for postdoctoral fellows, residents and medical students. A well-coordinated and integrated clinical and translational research training program has been developed utilizing the diverse trans-institutional faculty and other resources for teaching and mentoring.

Your research is important to the CTSC and I offer you our full support.

Sincerely,

A handwritten signature in black ink, appearing to read "Julianne Imperato-McGinley".

Julianne Imperato-McGinley, MD
Associate Dean, Translational Research and Education
Program Director, Clinical and Translational Science Center
Abby Rockefeller Mauzé Distinguished Professor of Endocrinology in Medicine



November 1, 2023

Chani Traube, MD, FAAP, FCCM
Professor of Pediatrics
Division of Pediatric Critical Care Medicine
Weill Cornell Medicine
525 East 68th St, M-508
New York, NY 10065

Clinical and Translational Science Institute
Building 379, Rm. 220
27 S. Mario Capecchi Dr.
Salt Lake City, Utah 84132
Office: 801.581.6736

Dear Dr. Traube:

As co-Directors of the Utah Clinical and Translational Science Institute (CTSI), we are pleased to enthusiastically support your application for the HEAL KIDS program titled “Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM).” You have designed a large RCT to address an important unmet need in children with acute respiratory failure. These children currently receive high-dose opioids, yet experience episodes of pain. You have assembled a well-qualified and impressive team to evaluate the effectiveness of supplementing opioids with acetaminophen and/or ketorolac to reducing acute pain and decrease opioid exposure. The Utah Data Coordinating Center (Utah DCC) has extensive expertise leading research programs in critically ill children.

Supported by a Clinical & Translational Science Award through the National Center for Advancing Translational Science, the Utah CTSI builds on the University of Utah’s research strengths to translate promising discoveries into practices that improve human health. We facilitate this by providing investigators with the facilities, resources and collaborations they need to effectively conduct translational research studies. The success of the Utah CTSI, due in part to our established collaborations with the Veteran’s Affairs (VA) Salt Lake City Health Care System, the Utah Department of Health and Human Services, Comagine, Intermountain Health, University of Nevada, Reno, the Association for Utah Community Health, and Community Faces of Utah, allows us to provide multiple resources to enhance this strong research proposal. We are committed to providing you and your research team full access to the Utah CTSI services, as needed for your project.

The CTSI’s **Clinical Research Support Office (CRSO)** is the central hub to provide support across the lifecycle of a clinical research study. It enhances compliance, reduces administrative burdens, and helps remove barriers to enable efficiency, internal/external collaboration, cost recovery, and growth of clinical trials. CRSO provides navigation, tools, services, and training to support clinical research, and coordinates with existing departmental clinical research units. It is the administrative home for the clinical trial management system, OnCore, as well as Epic Research. It provides IND/IDE support, and central monitoring, and quality assurance services.

The CTSI’s **Community Collaboration and Engagement Team (CCET)** provides the research team expertise through their patient advocate program that has a history of creating and utilizing innovative tools to collaborate and engage research participants through partnership in research. The CCET will be able to provide the team the necessary resources to successfully involve diverse populations.

The CTSI also collaborates with the UU Vice President for Research though the **Research Ethics Service (RES)**. RES provides formal training, educational materials, and consultative services to promote scientific integrity, rigor, and the responsible conduct of research across the institution.

The Utah CTSI looks forward to supporting your project. We wish you every success on your application.

Sincerely,

A handwritten signature in black ink that appears to read "Rachel Hess".

Rachel Hess, MD, MS
Associate Vice President for Research, Health Sciences
Professor of Population Health Sciences and Internal Medicine
H.A. and Edna Benning Presidential Endowed Chair
Co-Director, Utah Clinical and Translational Science Institute
University of Utah

A handwritten signature in black ink that appears to read "Jennifer Juhl Majersik".

Jennifer Juhl Majersik, MD, MS, FAHA, FAAN
Professor of Neurology
Chief, Division of Vascular Neurology
Director, UUH Stroke Center
Co-Director, Utah Clinical and Translational Science Institute
Associate Dean, Clinical and Translational Science
University of Utah



Stony Brook Children's

School of Medicine
Department of Pediatrics

October 25, 2023

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics, Weill Cornell Medicine

Michael Bell, MD
Division Chief, Critical Care Medicine
Children's National Medical Center

Richard Holubkov, PhD
Chief Biostatistician, CPCCRN
Professor of Pediatrics, University of Utah

Dear Chani, Michael, And Rich,

I look forward to working with you as a Medical Monitor for your HEAL Initiative Clinical Trials Program, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**", in response to RFA-HD-24-011.

As an experienced pediatric critical care provider, I am well-aware of the need to optimize management of acute pain in children on invasive mechanical ventilation. I am enthusiastic about your randomized controlled trial that will be the first to ever investigate the effects of the opioid adjuncts, acetaminophen, and ketorolac, in children with acute respiratory failure. If your hypothesis is proven, this can revolutionize the care we provide to critically ill children. However, I am also well-aware of the need for meticulous safety monitoring in this high-risk population. Therefore, I am committed to serve as Medical Monitor for this study.

In this role, I will help ensure the safety and wellbeing of study subjects throughout the trial. I will:

- Review study design prior to initiation of enrollment
- Review serious adverse events.
- Provide medical support when questions arise from the project team or clinical sites.
- Attend steering committee meetings on an ad hoc basis.

My hourly rate is \$200/hour, and I anticipate that the above outlined services will require 50 hours/year.

I look forward to working with you on this very interesting study, which I believe will contribute important data to improve the care of critically ill, mechanically ventilated children.

Sincerely,

A handwritten signature in blue ink that reads "Margaret M. Parker".

Margaret M. Parker, MD, MCCM
Professor Emerita of Pediatrics
Stony Brook University



1 Children's Way, Slot 512-2
Little Rock, AR 72202-3591
MAIN: 501-364-1846
FAX: 501-364-3188

Ronald C. Sanders, Jr MD, MS

Professor Critical Care
Section Chief

Abdallah Dalabih, MD, MBA
Professor

October 30, 2023

Xiomara Garcia-Casal, MD
Professor

M. Michele Moss, MD
Professor

Peter Mourani, MD
Professor

Parthak Prodhani, MD, MBBS
Professor

Stephen Schexnayder, MD
Professor

Michael H. Stroud, MD
Professor

Brian Varisco, MD,
Professor

Katherine Irby, MD
Associate Professor

Matthew P. Malone, MD
Associate Professor

Sanjiv Pasala, MD
Associate Professor

Rupal Bhakta, MD
Associate Professor

Erin Bennett, MD
Assistant Professor

Courtney Cox, MD
Assistant Professor

Diedre Wyrick, MD
Assistant Professor

Kristen Long, MD
Assistant Professor

S. Nathan Epps, MD
Assistant Professor

Salim Aljabari, MD
Assistant Professor

James G. Williams, MD
Assistant Professor

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine
525 E. 68th St., M-508
New York, NY 10065

Dear Dr. Traube:

It is my pleasure to support your HEAL KIDS Initiative Clinical Trials Program, "**Optimizing Pain Treatment in Children on Mechanical Ventilation (OPTICOM)**", in response to RFA-HD-24-011. This study will help to advance the treatment of acute pain in a diverse population of children across the age spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

Importantly, we applaud the inclusion of varied perspectives in the development of this research plan. We are grateful for the wide array of expertise represented by the key investigators, and – most importantly -- involvement of family stakeholders from diverse racial, ethnic, socioeconomic, and geographic populations. We join you in your commitment to maximize the enrollment of patients who are often under-represented in pediatric research.

The Collaborative Pediatric Critical Care Research Network (CPCCRN) has provided an infrastructure to strive for the reduction of some of the biggest challenges in the area of pediatric critical illness and injury, illuminating best practices through clinical and translational science. As a CPCCRN clinical participation site, we can quickly enroll using the existing resources established within the network.

Should the project be funded, we intend to invoice your institution for startup and maintenance fees (\$5,000 in year 1), annual Pharmacy storage costs (up to \$2500 per year), and a capitation fee per enrollment (\$6,000 per enrollment, includes the cost of study drugs and dispensing fees for the investigational pharmacy). In return, we will identify and enroll eligible patients, collect and provide clinical data, and complete the Common Data Elements required by the HEAL initiative. We also understand that the final budget will be dependent on the NIH and Steering Committee in this cooperative U01 award.

Page Two

By expanding HEAL-KIDS research into this unique and unstudied population, this project will lead to a paradigm shift in the acute pain management provided to critically ill children with acute respiratory failure. I look forward to continuing our collaboration to improve pediatric critical care for future generations.

Sincerely,



Ron C. Sanders, Jr., MD, MS, FAAP, FCCM
Chief, Section of Critical Care, Department of Pediatrics
President-elect, UAMS Academic Senate
Medical Director, Pediatric Intensive Care Unit, Arkansas Children's Hospital
Medical Director, Respiratory Care Services, Arkansas Children's Hospital
College of Medicine, University of Arkansas for Medical Sciences
1 Children's Way, Slot 512-12 * Little Rock, AR 72202-3591
Office Manager (Angie McCuin) * Phone: 501-364-1846
mccuinangiem@uams.edu



Division of Critical Care Medicine

Michael Bell, MD

Division Chief and Endowed Chair

Sonali Basu, MD

Associate Division Chief for Education

Fellowship Program Director

Matthew Sharron, MD

Medical Director, PICU

Faculty

Emily Abbey, CPNP-AC

Susan Conway, MD

Christiane Corriveau, MD

Lexi McBride Crawford, MD

Terry Dean, MD PhD

Elizabeth Claire Elliott, MD

Divya Gupta, MD

Aadil Kakajiwala, MD

Esther J. Kim, MD

Amy Jones, MD

Jia Liu, MD

Vanessa Madrigal, MD

Nada Mallick, MD

Marisa Mize, MSN, CPNP-AC

Taylor Olson, MD

Akilah Pascall, MBBS, FAAP

Anita Patel, MD

Murray Pollack, MD

Matthew Sharron, MD

Michael Shoyhet, MD PhD

Eduardo Trujillo-Rivera, PhD

Kitman Wai, MD

Mekela Whyte-Nesfield, MD

PICU Telephone 202-476-2010

PICU Fax 202-476-3238

Chani Traube, MD, FAAP, FCCM
Principal Investigator, OPTICOM Trial
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

It is my pleasure to support your HEAL KIDS Initiative Clinical Trials Program, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**", in response to RFA-HD-24-011. This study will help to advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

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We understand that the current funding includes our ability to invoice your institution for startup and maintenance fees (\$5,000 in year 1), annual Pharmacy storage costs (up to \$2500 per year), and a capitation fee per enrollment (\$6,000 per enrollment, includes the cost of study drugs and dispensing fees for the investigational pharmacy). In return, we will identify and enroll eligible patients, collect and provide clinical data, and complete the Common Data Elements required by the HEAL initiative. We also understand that the final budget will be dependent on the NIH and Steering Committee in this cooperative U01 award.

As part of the OPTICOM trial, we are committed to the development of the next generation of physician scientists. Therefore, we have chosen Drs. Nada Mallick and Elizabeth Elliott to serve in the role of site PI at Children's National. Dr. Mallick has been involved in the Pediatric Delirium R01 since its inception, and Dr. Elliott is a mentee of Dr. Bell, CNH MPI of OPTICOM. We believe that our contribution to CPCCRN and OPTICOM will be a wonderful asset to the project, to include multiple points of view and ensure the growth of young clinician scientists for the field of pediatric critical care in the future.



By expanding HEAL-KIDS research into this unique and unstudied population, this project will lead to a paradigm shift in the acute pain management provided to critically ill children with acute respiratory failure. I look forward to continuing our collaboration to improve pediatric critical care for future generations.

Please let us know of any assistance we can provide for the completion of this application and we look forward to the successful launch of OPTICOM in the coming months.

Sincerely,

A handwritten signature in black ink that appears to read "Nada Mallick".

Nada Mallick, MD
Pediatric Critical Care Medicine,
Children's National Hospital
Assistant Professor, George Washington
University School of Medicine

A handwritten signature in black ink that appears to read "Elizabeth Elliott".

Elizabeth Elliott, MD
Pediatric Critical Care Medicine, Children's
National Hospital
Assistant Professor, George Washington
University School of Medicine

gn



October 30, 2023

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

It is my pleasure to support your HEAL KIDS Initiative Clinical Trials Program, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**", in response to RFA-HD-24-011. This study will help to advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

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Should the project be funded, we intend to invoice your institution for startup and maintenance fees (\$5,000 in year 1), annual Pharmacy storage costs (up to \$2500 per year), and a capitation fee per enrollment (\$6,000 per enrollment, includes the cost of study drugs and dispensing fees for the investigational pharmacy). In return, we will identify and enroll eligible patients, collect and provide clinical data, and complete the Common Data Elements required by the HEAL initiative. We also understand that the final budget will be dependent on the NIH and Steering Committee in this cooperative U01 award.

As part of the **OPTICOM** program, we are committed to the development of the next generation of physician scientists. Therefore, we have chosen Dr. Tageldin Ahmed to serve in the role of site PI at Central Michigan University/Children's Hospital of Michigan. Dr. Ahmed is Assistant Professor of Pediatrics, and will be a wonderful asset to the project. I am committed to providing mentorship to Dr. Ahmed in every way, in order to foster his/her growth as a clinical scientist and ensure the successful completion of this study.

By expanding HEAL-KIDS research into this unique and unstudied population, this project will lead to a paradigm shift in the acute pain management provided to critically ill children with acute respiratory failure. I look forward to continuing our collaboration to improve pediatric critical care for future generations.



Sincerely,

Kathleen Meert, MD

Kathleen Meert, MD
Schotanus Family Professor & Chair
Discipline of Pediatrics
Central Michigan University
Specialist-in-Chief, Pediatrics
Children's Hospital of Michigan
Detroit Medical Center



11-3-2023

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

It is my pleasure to support your HEAL KIDS Initiative Clinical Trials Program, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**", in response to RFA-HD-24-011. This study will help to advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

Importantly, we applaud the inclusion of varied perspectives in the development of this research plan. We are grateful for the wide array of expertise represented by the key investigators, and – most importantly -- involvement of family stakeholders from diverse racial, ethnic, socioeconomic, and geographic populations. We join you in your commitment to maximize enrollment of patients who are often under-represented in pediatric research.

The Collaborative Pediatric Critical Care Research Network (CPCCRN) has provided an infrastructure to strive for the reduction of some of the biggest challenges in the area of pediatric critical illness and injury, illuminating best practice through clinical and translational science. As a CPCCRN clinical participation site, we can quickly enroll using the existing resources established within the network.

Should the project be funded, we intend to invoice your institution for startup and maintenance fees (\$5,000 in year 1), annual Pharmacy storage costs (up to \$2500 per year), and a capitation fee per enrollment (\$6,000 per enrollment, includes the cost of study drugs and dispensing fees for the investigational pharmacy). In return, we will identify and enroll eligible patients, collect and provide clinical data, and complete the Common Data Elements required by the HEAL initiative. We also understand that the final budget will be dependent on the NIH and Steering Committee in this cooperative U01 award.

By expanding HEAL-KIDS research into this unique and unstudied population, this project will lead to a paradigm shift in the acute pain management provided to critically ill children with acute respiratory failure. I look forward to continuing our collaboration to improve pediatric critical care for future generations.

Sincerely,

A handwritten signature in black ink, appearing to read "Adam J Schwarz".

Adam J Schwarz, MD
Director, Clinical Research
Division of Pediatric Critical Care, Pediatric Subspecialty Faculty
CHOC Children's
Associate Clinical Professor Pediatrics, University of California, Irvine, School of Medicine

LONG LIVE CHILDHOOD



October 22, 2023

Chani Traube, MD, FAAP, FCCM

Chair, CPCCRN Steering Committee

Professor of Pediatrics

Weill Cornell Medicine

Dear Dr. Traube,

It is my pleasure to enthusiastically support your HEAL KIDS Initiative Clinical Trials Program, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**," in response to RFA-HD-24-011. This study will advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

Importantly, we applaud the inclusion of varied perspectives in the development of this research plan. We are grateful for the wide array of expertise represented by the key investigators, and – most importantly -- involvement of family stakeholders from diverse racial, ethnic, socioeconomic, and geographic populations. We join you in your commitment to maximize enrollment of patients who are often under-represented in pediatric research.

The Collaborative Pediatric Critical Care Research Network (CPCCRN) has provided an infrastructure to strive for the reduction of some of the biggest challenges in pediatric critical illness and injury, illuminating best practice through clinical and translational science. As a CPCCRN clinical participation site, we have established over the last 14 years that we can quickly enroll using the existing resources established within the network.

Should the project be funded, we intend to invoice your institution for startup and maintenance fees (\$5,000 in year 1), annual Pharmacy storage costs (up to \$2500 per year), and a capitation fee per enrollment (\$6,000 per enrollment, which includes the cost of study drugs and dispensing fees for the investigational pharmacy). In return, we will identify and enroll eligible patients, collect and provide clinical data, and complete the Common Data Elements required by the HEAL initiative. We also understand that the final budget will be dependent on the NIH and Steering Committee in this cooperative U01 award.

As part of the **OPTICOM** program, we are committed to the development of the next generation of physician scientists. Therefore, we have chosen Dr. Wolfe to serve in the role of site PI at The Children's Hospital of Philadelphia. Dr. Wolfe has been one of my Critical Care Medicine fellows and then a junior faculty mentee of mine for more than a decade. Dr. Wolfe is an Associate Professor in Anesthesiology and Critical Care Medicine and will be a wonderful asset to the project. I am committed to providing mentorship to Dr. Wolfe in every way, in order to foster her growth as a clinical scientist and ensure the successful completion of this study.

By expanding HEAL-KIDS research into this unique and unstudied population, this project will lead to a paradigm shift in the acute pain management provided to critically ill children with acute respiratory failure. I look forward to continuing our collaboration to improve pediatric



critical care for future generations.

In summary, I enthusiastically support this project and commit **The Children's Hospital of Philadelphia** to be a dedicated site with **me and Dr. Wolfe** as **site PIs**, and with me mentoring Dr. Wolfe in this new role for her.

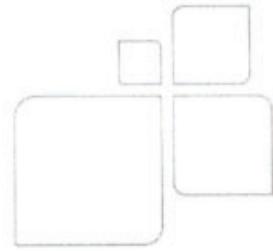
A handwritten signature in black ink, appearing to read "Robert A. Berg".

Robert A. Berg, M.D., MCCM, FAAP, FAHA

Professor of Anesthesia and Critical Care Medicine and Professor of Pediatrics

The University of Pennsylvania Perelman School of Medicine

Children's Hospital of Philadelphia



Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

It is my pleasure to support your HEAL KIDS Initiative Clinical Trials Program, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**", in response to RFA-HD-24-011. This study will help to advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

Importantly, we applaud the inclusion of varied perspectives in the development of this research plan. We are grateful for the wide array of expertise represented by the key investigators, and – most importantly -- involvement of family stakeholders from diverse racial, ethnic, socioeconomic, and geographic populations. We join you in your commitment to maximize enrollment of patients who are often under-represented in pediatric research.

The Collaborative Pediatric Critical Care Research Network (CPCCRN) has provided an infrastructure to strive for the reduction of some of the biggest challenges in the area of pediatric critical illness and injury, illuminating best practice through clinical and translational science. As a CPCCRN clinical participation site, we can quickly enroll using the existing resources established within the network.

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By expanding HEAL-KIDS research into this unique and unstudied population, this project will lead to a paradigm shift in the acute pain management provided to critically ill children with acute respiratory failure. I look forward to continuing our collaboration to improve pediatric critical care for future generations.

A handwritten signature in blue ink, appearing to read "MS".

Mohammed Salameh, MD
Assistant Professor, Pediatric Critical Care
CHRISTUS Children's
Baylor College of Medicine

333 N. Santa Rosa Street
San Antonio, TX 78207
T: 000.000.0000
CHRISTUSchildrens.org

Your children. Your family. Our purpose.



John M. Costello, MD, MPH
Vice Chair of Clinical Research, Department of Pediatrics
Director of Research, Children's Heart Center
Professor of Pediatrics
Medical University of South Carolina
165 Ashley Avenue, MSC 915
Charleston SC 29425
costello@musc.edu
Tel 843-792-9570
MUSCKids.org

October 25, 2023

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

It is my pleasure to support your HEAL KIDS Initiative Clinical Trials Program, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**", in response to RFA-HD-24-011. This study will help to advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

Importantly, we applaud the inclusion of varied perspectives in the development of this research plan. We are grateful for the wide array of expertise represented by the key investigators, and – most importantly -- involvement of family stakeholders from diverse racial, ethnic, socioeconomic, and geographic populations. We join you in your commitment to maximize enrollment of patients who are often under-represented in pediatric research.

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As part of the **OPTICOM** program, we are committed to the development of the next generation of physician scientists. Therefore, we have chosen Dr. Austin Biggs to serve in the role of site PI at MUSC. Dr. Biggs is an Assistant Professor of Pediatrics and a pediatric intensivist. He will be a wonderful asset to the project. I am committed to providing mentorship to Dr. Biggs in every way, in order to foster his growth as a clinical scientist and ensure the successful completion of this study.

By expanding HEAL-KIDS research into this unique and unstudied population, this project will lead to a paradigm shift in the acute pain management provided to critically ill children with acute respiratory failure. I look forward to continuing our collaboration to improve pediatric critical care for future generations.

Sincerely,

A handwritten signature in black ink, appearing to read "John M. Costello".

John M. Costello, M.D., M.P.H.
Vice Chair of Clinical Research, Department of Pediatrics
Director of Research, Children's Heart Center
Interim Division Chief, Pediatric Critical Care Medicine
Professor of Pediatrics, Medical University of South Carolina

"Imagine Healthier Children."



October 24, 2023

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

It is my pleasure to support your HEAL KIDS Initiative Clinical Trials Program, “Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)”, in response to RFA-HD-24-011. This study will help to advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

We applaud the inclusion of varied perspectives in the development of this research plan. We are grateful for the wide array of expertise represented by the key investigators, and – most importantly – involvement of family stakeholders from diverse racial, ethnic, socioeconomic, and geographic populations. We join you in your commitment to maximize enrollment of patients who are often under-represented in pediatric research.

The Collaborative Pediatric Critical Care Research Network (CPCCRN) has provided an infrastructure to target some of the biggest challenges in the area of pediatric critical illness and injury, illuminating best practice through clinical and translational science. As a CPCCRN clinical participation site, we can quickly enroll subjects using the existing resources established within the network.

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As part of the OPTICOM program, we are committed to the development of the next generation of physician scientists. Therefore, we have chosen Dr. Ambrish Patel to serve in the role of site Co-I at Nationwide Children’s Hospital. Dr. Patel is a dual trained pediatric intensivist and pediatric anesthesiologist and is exceptionally well-suited to this project. I am committed to providing mentorship to Dr. Patel in order to foster his/her growth as a clinical scientist and ensure the successful completion of this study.

By expanding HEAL-KIDS research into this unique and unstudied population, this project will lead to a paradigm shift in the acute pain management provided to critically ill children with acute respiratory failure. I look forward to continuing our collaboration to improve pediatric critical care for future generations.

Sincerely,

Mark W. Hall, MD, FCCM
Professor of Pediatrics
Chief, Division of Critical Care Medicine
Nationwide Children’s Hospital
The Ohio State University College of Medicine
Columbus, OH 43205 Phone: (614) 722 – 3438; E-mail: Mark.Hall@NationwideChildrens.org

700 Children's Drive | Columbus, Ohio 43205 | 614.722.2000 | NationwideChildrens.org



Ayse Akcan Arikan, M.D.

Associate Professor, Pediatrics - Critical Care Medicine
Medical Director, Extracorporeal Liver Support
Medical Director, Critical Care Nephrology

October 30, 2023

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

It is my pleasure to support your HEAL KIDS Initiative Clinical Trials Program, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**", in response to RFA-HD-24-011. This study will help to advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

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Letter of Support - Dr. Traube
Continued – Page Two

By expanding HEAL-KIDS research into this unique and unstudied population, this project will lead to a paradigm shift in the acute pain management provided to critically ill children with acute respiratory failure. I look forward to continuing our collaboration to improve pediatric critical care for future generations.

Sincerely,



Ayse Akcan Arikan, M.D.
Associate Professor of Pediatrics
Baylor College of Medicine
Divisions of Renal and Critical Care Medicine
Medical Director, Extracorporeal Liver Support
Medical Director, Critical Care Nephrology
Texas Children's Hospital



Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

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Sincerely,

A handwritten signature in black ink that appears to read "Steven L. Shein, MD".

Steven L. Shein, MD
Chief of Pediatric Critical Care Medicine
Linsalata Family Chair in Pediatric Critical Care and Emergency Medicine
Director, Pediatric Critical Care Medicine Fellowship Program
Co-Director, Pediatric Critical Care Clinical, Basic & Translational Research Program
Rainbow Babies and Children's Hospital
Associate Professor of Pediatrics
Case Western Reserve University
Cleveland, Ohio
Steven.shein@uhhospitals.org

Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

It is my pleasure to support your HEAL KIDS Initiative Clinical Trials Program, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**", in response to RFA-HD-24-011. This study will help to advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

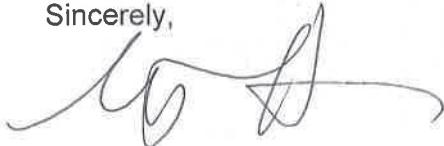
Importantly, we applaud the inclusion of varied perspectives in the development of this research plan. We are grateful for the wide array of expertise represented by the key investigators, and – most importantly -- involvement of family stakeholders from diverse racial, ethnic, socioeconomic, and geographic populations. We join you in your commitment to maximize enrollment of patients who are often under-represented in pediatric research.

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Should the project be funded, we intend to invoice your institution for startup and maintenance fees (\$5,000 in year 1), annual Pharmacy storage costs (up to \$2500 per year), and a capitation fee per enrollment (\$6,000 per enrollment, includes the cost of study drugs and dispensing fees for the investigational pharmacy). In return, we will identify and enroll eligible patients, collect and provide clinical data, and complete the Common Data Elements required by the HEAL initiative. We also understand that the final budget will be dependent on the NIH and Steering Committee in this cooperative U01 award.

By expanding HEAL-KIDS research into this unique and unstudied population, this project will lead to a paradigm shift in the acute pain management provided to critically ill children with acute respiratory failure. I look forward to continuing our collaboration to improve pediatric critical care for future generations.

Sincerely,



Moonjoo Han, MD
Associate Professor
Division of Critical Care Medicine
Department of Pediatrics
UC Davis Children's Hospital
2516 Stockton Boulevard
Sacramento, CA 95817

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

November 11, 2023

**Pediatric Critical
Care
Medicine**

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Chani Traube, MD, FAAP, FCCM
Chair, CPCCRN Steering Committee
Professor of Pediatrics
Weill Cornell Medicine

Dear Dr. Traube,

It is my pleasure to support your HEAL KIDS Initiative Clinical Trials Program, "**Optimizing Pain Treatment In Children On Mechanical ventilation (OPTICOM)**", in response to RFA-HD-24-011. This study will help to advance the treatment of acute pain in a diverse population of children across the age-spectrum and advance the ultimate goal of developing comprehensive evidence-based clinical guidelines for management of pain in children with acute respiratory failure.

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Joseph A. Carcillo, MD
Children's Hospital of Pittsburgh
University of Pittsburgh School of Medicine

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Jill Sweeney, MD MBA
Associate Professor Pediatrics
Division Chief Pediatric Critical Care
295 Chipeta Way
Salt Lake City UT 84108



Division of Pediatric Critical Care Medicine
Department of Pediatrics

Chani Traube, MD, FAAP, FCCM
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Sincerely,

A handwritten signature in black ink, appearing to read "Nikki Miller Ferguson".

Nikki Miller Ferguson, MD
Associate Medical Director of PICU
Medical Director of Pediatric Transport
Associate Professor, Dept. of Pediatrics
Division of Critical Care
Children's Hospital of Richmond, VCU
Nikki.millerferguson@vcuhealth.org

RESOURCE SHARING PLAN

We will follow the guidance of NOT-OD-16-149 NIH Policy on the Dissemination of NIH Funded Clinical Trial Information (or any relevant document that replaces this guidance). We are committed to sharing our study data with the public and will do so within two years of the end of the project period (or as per contemporaneous policy). For example, we would look for HEAL-compliant data repositories to deposit our datasets, such as NICHD DASH, NIDA Data Share to ensure the data is accessible via the HEAL Initiative Data Ecosystem.

All the participating OPTICOM researchers have made a commitment to publish, in a timely manner, all the relevant scientific information that they will derive during this project. Data and other resources developed by the proposed project will be shared through peer-reviewed scientific journals publications made available through **PubMedCentral** as well as through appropriate websites/databases in accordance with the **HEAL Public Access and Data Sharing policy**, and other collaborative and service opportunities in accordance with NIH guidelines and recommendations.

The overall objectives of our sharing plan are to: (1) Ensure that datasets and resources will be widely shared with the scientific community and public to extend research and training; and (2) Ensure the long-term value, reliability, and capability for reuse of data sets collected through program-wide data curation, stewardship, and archiving. The **Data Coordinating Center (DCC)** will coordinate and manage the shared research data.

Dr. Traube will serve as the point of contact for investigators seeking data or resources developed through OPTICOM. After publication, it is also expected that specific requests may be made instead to the corresponding author of the relevant publication(s) (i.e., Drs. Traube, Bell, Hoblukov, or other key personnel, depending on the nature of the publication).

The PIs strongly believe that NIH-funded (i. e., taxpayer-funded) research should be “open source.” As such, they are well known in the community for openly sharing resources, protocols, and also for publishing in-depth “materials and methods” information of their published work. The results and methods of this project will be published in a timely manner. The PIs will gladly comply with any further specific resource- and data sharing plans, as may be required by NIH.

Sharing model organisms

The OPTICOM team will not generate any model organisms. However, this Program does expect to generate other kinds of novel research resources (i.e.: datasets) of potential use to others.

NIH Generated message:

The Other Plan(s) attachment included with the application is not evaluated during the peer review process but will be evaluated prior to a funding decision. Although part of the official submission, the attachment is maintained as a separate document in eRA Commons viewable by authorized users and is not part of this assembled application.

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

Each clinical site's Investigational Pharmacy will provide the following standard treatment medications:

1. Acetaminophen 15 mg/kg* IV q 6 hours (max dose 1 g) and,
2. Ketorolac 0.5 mg/kg IV q 6 hours (max dose 30 mg)

The investigational pharmacy at Children's National Medical Center will serve as the central pharmacy for the OPTICOM study. They will develop source documentation, pharmacy training materials, operating manuals, and study-specific pharmacy procedures as needed. Clinical sites' investigational pharmacies (IP) will be responsible for storage of study drugs, and documentation of lot numbers and expiration information. The site IP will facilitate blinding, and prepare placebo doses, all of which will consist of normal saline infusions of equivalent volume to the study drugs. The clinical site pharmacy will maintain adequate records of all dispensed study drugs. Each pharmacy will be monitored (both on-site and with remote visits) and may be requested to send copies of documents to the Data Coordinating Center and/or the investigational pharmacy at CNMC which will conduct remote audits at regular intervals.

(*for children <28 days old, dose will be 12.5 mg/kg IV q 6 hours as per FDA recommendations)