

Project Summary

Approximately 7.7% of the United States population are self-reported Asian American (AsA), Native Hawaiian, or Pacific Islander (NHPI). AsA and NHPI include over 40 culturally distinct race and ethnic groups which are typically aggregated in population research. Inappropriate aggregation obscures health disparities in these communities since many chronic health conditions differ among the groups. The Utah Data Coordinating Center (DCC) is applying to serve as the Coordinating Center (CC) for the AsA-NHPI Cohort Study, which was developed to identify population health gaps in these communities. The Utah DCC will provide the infrastructure to aid understanding of sociocultural, environmental, psychological health, and lifestyle dimensions, in addition to quantifying and evaluating metabolic, cardiovascular, lung, cancer, and aging diseases in AsA and NHPI communities. The Multiple Principal Investigators Drs. Dwyer, VanBuren, and Raphael will provide internationally recognized leadership. Dr. Dwyer has expertise in multi-center research, Dr. VanBuren will provide sophisticated biostatistical leadership, and Dr. Raphael, a Native Hawaiian, is a clinical and translational scientist, community activist, and leader who will provide culturally sensitive context to the CC efforts and deep connections to the NHPI population. The Utah DCC will provide overall management, coordination, communication, leadership, and support of the AsA-NHPI Cohort Study across the entirety of the project. We will develop and pilot the protocol across all the sites during the UG3 phase and implement it during the UH3 phase. We will design and implement the cohort study utilizing the following Specific Aims:

Specific Aim 1. Coordinate with the Clinical/Community Field Centers (CCFC) and the Project Officers to provide *independent* clinical and biostatistical leadership and expertise to establish the culturally sensitive network infrastructure with key cross-study committees, develop necessary materials including the protocol/training plans and data collection tools, and direct the logistics of site capitated payments for data/biospecimen collection.

Specific Aim 2. Collect and harmonize phenotypic data using common data elements and standardized assessments utilizing our existing DCC infrastructure to ensure data integrity, security, and sovereignty of collected populomic data, including biospecimens via a dedicated central laboratory and biorepository.

Specific Aim 3. Provide an analytical and dissemination infrastructure, including implementing processes for timely data analyses, tracking publications, assisting with future funding opportunities, and managing outward-facing materials such as a public/participant and investigator website, data book, newsletter, and public-use dataset suitable for deposit in NHLBI repositories.

The Utah DCC has the necessary clinical and biostatistical expertise at every stage of study development and implementation to coordinate the AsA-NHPI Cohort Study.

Project Narrative

The University of Utah is applying to function as the Coordinating Center for the Asian American, Native Hawaiian, and Pacific Islander Cohort Study to support the enrollment, initial exam, and follow-up activities. Our team is well positioned to bring culturally sensitive context, biostatistical, clinical, and cohort management leadership to the network. We will guide the network in creating an implementable protocol during startup to enable successful transition to the enrollment phase and cohort management leadership to deliver a scientifically informative cohort study in these populations.

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Facilities and Other Resources

A University of Utah Data Coordinating Center

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), implementing over 140 active or completed multi-center studies (Table 2) resulting in over 500 publications through August 2022.

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 (AHCERN) | 2013 |
| Fetal Heart Society (FHS) | 2014 |
| Pediatric Colorectal and Pelvic Learning Consortium (PCPLC) | 2016 |
| Four Corners Youth Concussion Research Network | 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) ^{1–9} | > 20 million (visits) | Completed |
| The Effectiveness of Oral Dexamethasone for Acute Bronchiolitis: A Multicenter, Randomized Controlled Trial (R40MC04298) ^{10,11} | 598 | Completed |
| Hypothermia for Pediatric Cardiac Arrest Planning Grant (R21HD044955) ^{12–17} | 491 | Completed |
| Planning Hypothermia Trial for Pediatric Cardiac Arrest (R34HD050531) | Not applicable | Completed |
| Childhood Head Trauma: A Neuroimaging Decision Rule (R40MC02461) ^{18–35} | 42,412 | Completed |
| Predicting Cervical Spine Injury (CSI) in Children: A Multi-centered Case-Control Analysis ^{36–39} | 540 | Completed |
| A Diagnosis Grouping System for Child ED Visits ^{40–43} | Not applicable | Completed |
| A Clinical Decision Rule to Identify Children with Intra-abdominal Injuries ^{44–46} | 12,044 | Completed |
| CPCCRN Core Data Project (CCDP) | 249,306 (admissions) | Completed |
| Bereavement: Parents' Opinions on Physician Conference ^{47–50} | 56 (parents) | Completed |
| Development of a Quantitative Functional Status Scale (FSS) for Pediatric Patients ^{51,52} | 856 | Completed |
| Bereavement: Prevalence and Risk Factors for Complicated Grief in Parents ^{53–57} | 261 (parents) | Completed |
| The Critical Illness Stress-induced Immune Suppression (CRISIS) Prevention Trial ^{58–64} | 293 | Completed |
| Development of Research Partnerships with EMS Agencies and Descriptive Study of EMS Pediatric Population within PECARN ⁶⁵ | Not applicable | Completed (16 agencies, 514,880 individuals) |
| Patient Safety Procedures and Climate of Safety in Pediatric Emergency Departments ^{66–68} | Not applicable | Completed (29,000 incidents in 19 hospitals) |
| Referral and Utilization Patterns for Psychiatric Related Visits to the Pediatric ED ^{69,70} | 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 ^{71,72} | 70 (physicians) | Completed |
| Cortisol Quantification Investigation: Prospective, Observational Study of Free versus Total Serum Cortisol in PICU Patients ^{73,74} | 165 | Completed |
| Critical Pertussis in U.S. Children: Severe Morbidity, Sequelae and Mortality: A Prospective Cohort Study ^{75–78} | 225 | Completed |
| Measuring Opioid Tolerance Induced by Fentanyl (MOTIF) ^{79,80} | 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 ⁸¹ | 6,014 | Completed |
| Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA Trials) (U01HL094345, U01HL094339) ^{82–116} | 299 out-of-hospital; 334 in-hospital | Completed |
| Critical Asthma in the Pediatric Intensive Care Unit ^{117,118} | 261 | Completed |
| Phenotypes, Genomics, and Outcomes in Sepsis (POGOS) Recruitment Pilot ¹¹⁹ | 157 | Completed |

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Table 2: Multi-center Studies (*continued*)

| Name of Study | Participants Enrolled | Current Status |
|---|-----------------------|---|
| Bereavement: Pilot Study of Framework for Physician-Parent Follow-up Meetings ^{120–122} | 46 (interviews) | Completed |
| Trichotomous Outcome Prediction: Ideal Time Interval for Severity of Illness Assessment ¹²³ | 376 | Completed |
| Semantic Interoperability for CPCCRN Core Data Project ¹²⁴ | Not applicable | Completed |
| Hydrocephalus Clinical Research Network Pediatric Registry (R01NS068943) | 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) ^{125–128} | 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) ^{129, 130} | 4,797 | Completed |
| Fluid Therapy and Cerebral Injury in Pediatric Diabetic Ketoacidosis RCT (R01HD062417) ^{131, 132} | 1,255 | Completed |
| Implementation of the PECARN Traumatic Brain Injury Prediction Rules for Children Using Computerized Clinical Decision Support: an Interrupted Time Series Trial (ARRA S02MC19289) ¹³³ | 27,094 | 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) ^{134–137} | 208 | Completed |
| Translating an Adult Ventilator Computer Protocol to Pediatric Critical Care (R21HD061870) ^{138–141} | 120 | Completed |
| Trichotomous Outcome Prediction in Critical Care (TOPICC) ^{52, 142–149} | 10,080 | Completed |
| CPCCRN Informatics Initiative: picuGrid Project ¹⁵⁰ | Not applicable | Completed |
| Ventricular Size Involvement in Neuropsychological Outcomes in Pediatric Hydrocephalus | 72 | Enrolling |
| Cerebrospinal Fluid Markers of Post-Hemorrhagic Hydrocephalus | 92 | Enrolling |
| A Multicenter Retrospective Study of Endoscopic Third Ventriculostomy (ETV) and Choroid Plexus Cauterization (CPC) in Children with Hydrocephalus ¹⁵¹ | 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 ¹⁵² | 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 Feasibility for a RCT of Progesterone for Severe TBI | 298 | Completed |
| Planning a Multicenter Cooling Trial for Hyperammonemic Metabolic Crises (R34HD072101) | Not applicable | Completed |
| Bleeding and Thrombosis During ECMO - BATE ^{153–163} | 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)) ¹⁶⁴ | 17 | Completed |
| Impact of Emergency Department Probiotic Treatment of Pediatric Gastroenteritis RCT (R01HD071915) ^{165–173} | 971 | Completed |
| Impact of Hypothermia on Midazolam and Morphine Pharmacokinetics (R01HL112745) | 11 | Completed |
| Collaborative International Research in Clinical and Longitudinal Experience for Neuromyelitis Optica (CIRCLES) | 421 | Enrolling |
| Pediatric Intensive Care Quality of Cardiopulmonary Resuscitation (PICqCPR) ^{174–182} | 368 | Completed |
| An Open-label add-on of Cetirizine for Neuromyelitis Optica | 19 | Enrolling |
| Life after Pediatric Sepsis Evaluation - LAPSE (R01HD073362) ^{183–187} | 392 | Completed |
| Inflammation Phenotypes in Pediatric Sepsis Induced Multiple Organ Failure - PHENOMS (R01GM108618) ^{188–190} | 410 | Completed |
| 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) ¹⁹¹ | 400 | Accrual completed |

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Table 2: Multi-center Studies (*continued*)

| Name of Study | Participants Enrolled | Current Status |
|---|---------------------------|----------------|
| Sepsis Induced Red Cell Dysfunction (SIRD) (R01GM113838) | 175 | Completed |
| GM-CSF for Immunomodulation following Trauma (GIFT) (R01GM094203) | 117 | Completed |
| Inhaled Nitric Oxide Use in Pediatric Intensive Care ¹⁹² | 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 ¹⁹³ | 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) ¹⁹⁴ | 843 | Completed |
| RNA Biosignatures: A paradigm change for the management of young febrile infants (R01HD085233) | 2,612 | Completed |
| Informing the Research Agenda for Pediatric Intensive Care Units (IRA) ^{195–197} | 328 | Completed |
| Parent-Provider Alliance in Pediatric Intensive Care (PPA) | 233 (parents) | Completed |
| GM-CSF for Reversal of Immunoparalysis in Pediatric Sepsis-induced MODS (GRACE) | 40 | Completed |
| Improving Outcomes from Pediatric Cardiac Arrest (ICU-RESUS) (R01HL131544, R01HL147616) ¹⁹⁸ | 1,144 | Completed |
| 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) ¹⁹⁹ | 31 (interviews) | Completed |
| Acute Respiratory Distress Syndrome (ARDS) | 109 | Completed |
| Randomized Controlled Trial of Valgancyclovir for CMV-infected Hearing Impaired Infants (U01DC014706) | 10 | Completed |
| Childhood Radiologically Isolated Syndrome | 56 | 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 | Completed |
| Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children (R34HL135214) ^{200–205} | 31 | Completed |
| Improving Detection of STIs in the Pediatric ED: A Pragmatic Trial (R01HD094213) ^{206,207} | 134,597 | Enrolling |
| Effect of ED and after-ED Analgesic Treatment on Pediatric Long Bone Fracture Outcomes (R01HD091302) ²⁰⁸ | 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 Disease Pain (U01HL143477) ²⁰⁹ | 4,578 Visits in registry | Completed |
| 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 | 281 | Enrolling |
| 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) | 224 | Enrolling |
| 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 1:98, Phase 2:78 | Enrolling |
| Tailored Non-Pharmacotherapy Services for Chronic Pain: Testing Scalable and Pragmatic Approaches (UH3AG067493) | 1,163 | Enrolling |
| Effectiveness of an MHealth Psychosocial Intervention to Prevent Transition from Acute to Chronic Postsurgical Pain in Adolescents (UH3HD102038) | 82 | Enrolling |
| Integrated Treatment for Veterans with Co-Occurring Chronic Pain and Opioid Use Disorder (UH3DA051241) | 26 | Enrolling |
| Placebo Controlled Effectiveness in iNPH Shunting (PENS) Trial (U01NS122764) | 1 | Enrolling |
| Optimizing the Use of Ketamine to Reduce Chronic Post-surgical Pain (UH3CA261067) | 10 | Enrolling |

continued on next page

Table 2: Multi-center Studies (*continued*)

| Name of Study | Participants Enrolled | Current Status |
|--|-----------------------|----------------|
| 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) | 8 | 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 |
| Intravenous Magnesium: Prompt use for Asthma in Children Treated in the Emergency Department (1R34HL152047-01A1) | 2 | Enrolling |

A.1 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 20-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 who are highlighted here (Figure 1).

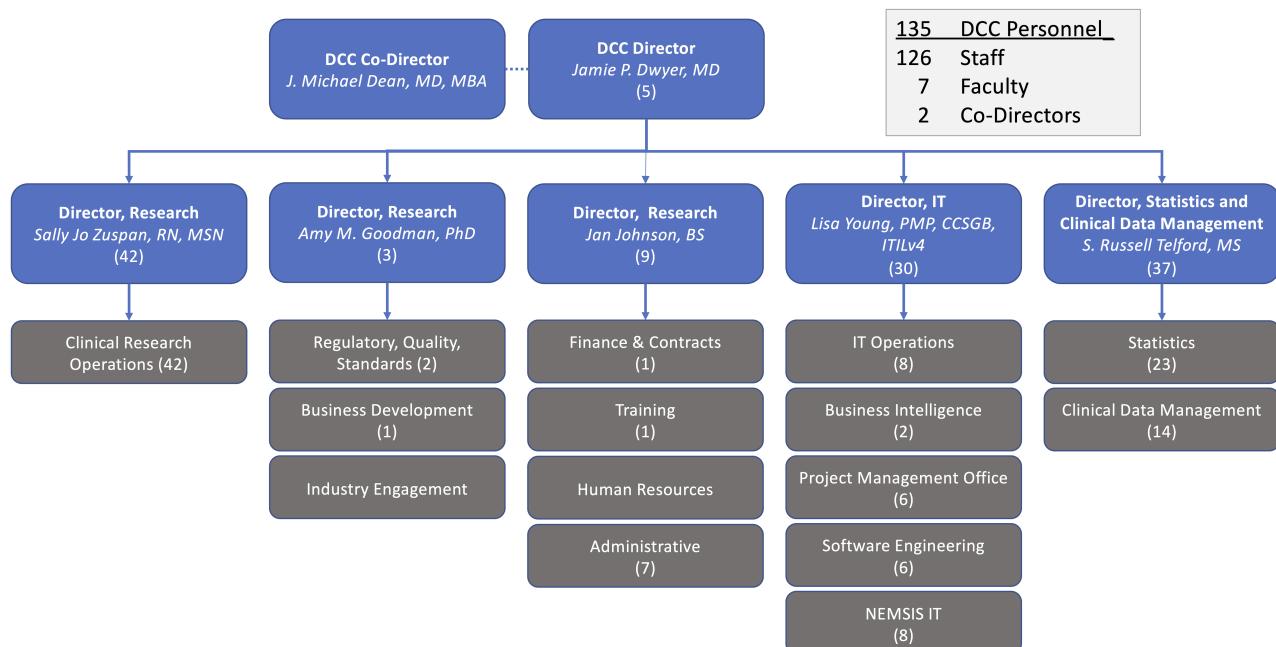


Figure 1: Organizational chart of the Utah Data Coordinating Center. Numbers in parentheses reflect number of staff. NEMESIS: National EMS Information System

Jamie P. Dwyer, MD directs the Utah DCC with **J. Michael Dean, MD, MBA** as Co-Director. Dr. Dwyer is an adult nephrologist with substantial experience in the development and management of large interventional clinical trials and is the current Director of the Clinical Research Support Office (CRSO) in the Clinical and Translational Science Institute (CTSI, described briefly in Section E), and is the Associate Dean for Clinical Research at the University of Utah School of Medicine. Dr. Dean established the DCC in 2001 and has extensive expertise with multi-center research. Drs. Dwyer and Dean provide senior consultation on study design, grant writing strategies, and implementation of projects coordinated by the Utah DCC. This senior medical leadership complements our biostatistical faculty and staff by facilitating scientific understanding and communication between the DCC and principal investigators (PI) of specific studies and trials.

John VanBuren, PhD is a member of the Utah DCC Executive Committee. He is a senior faculty biostatistician with substantial experience managing networks, providing data management supervision, study design and implementation, and creating study materials (e.g., protocol, analysis plans, data and observational safety monitoring reports). His statistical expertise is in Bayesian adaptive designs and other traditional statistical methods. Dr. VanBuren has a special interest in the use of risk-based monitoring (RBM) in academic, industry, and philanthropic studies to reduce the burden of the conduct of clinical research.

Sally Jo Zuspan, RN, MSN is a Director of Research (Operations) and member of the Utah DCC Executive Committee. She has 20 years of experience directing the DCC as well as overseeing multiple national research networks and multi-center research projects. She has managed, developed, or provided oversight for 60 clinical trials, registries, and observational studies. In prior years, she was a trauma program manager at a large children's hospital, a lobbyist who led legislative efforts in trauma care, and an emergency department nurse. Ms. Zuspan provides overall leadership and strategic direction to the DCC, oversees a staff of network and project directors, and mentors senior staff. She has spoken nationally in multiple research forums and specializes in training investigators and clinical research staff in how to avoid regulatory, data, and quality errors when conducting multi-center research. Ms. Zuspan has been active in developing risk-based quality initiatives and streamlining the conduct of clinical research.

Amy M. Goodman, PhD is a Director of Research (Business Development and Science) and member of the Utah DCC Executive Committee. Dr. Goodman is a clinical scientist and biomedical engineer with over fifteen years of experience designing and implementing multi-center interventional clinical studies, both in industry and within academic institutions. She is an expert in active implantable medical devices and taking products from the design and development stages through clinical testing and regulatory approval. She has held various engineering, clinical, and leadership positions in early-stage medical device companies, and as a consulting VP of Clinical and Regulatory Affairs, she has provided clinical research expertise for device companies. At the University of California, San Francisco (UCSF), Dr. Goodman directed the multi-center NIH-funded High Dose Erythropoietin for Asphyxia and Encephalopathy clinical coordinating center (PI: Yvonne Wu, U01NS092764). She also developed an institutional dashboard to enhance collaboration between operational units at UCSF. Dr. Goodman is an inventor of 11 issued patents, has authored a book chapter on the use of microstimulators for neuromodulation, and is an author on numerous peer-reviewed journal articles and conference abstracts. In her role at the University of Utah, Dr. Goodman provides overall leadership to the DCC, with a focus on supporting regulatory, quality, and standards initiatives and industry-funded studies and collaborations.

Jan Johnson, BS is a Director of Research (Finance and HR) and member of the Utah DCC Executive Committee. She has 10 years of experience directing the DCC with her main focus being human resources, finance, contracting, and administrative oversight. Prior to the DCC, Ms. Johnson co-directed the NIH-funded National Children's Study Vanguard site in Salt Lake and Utah Counties in Utah, and the Tri-Counties in Wyoming; and managed the Education Enterprise for the Department of Pediatrics. In her current role, Ms. Johnson provides overall DCC leadership and guidance, mentors senior and junior staff, and leads staffing, development, and retention efforts.

Lisa Young, PMP, CCSGB, ITILv4 is the IT Director and member of the Utah DCC Executive Committee. She has a combined 20 years of IT experience in the pharmaceutical industry and in clinical research. Ms. Young holds certifications in project management, cybersecurity, information assurance, IT service management, and Six Sigma. Prior to being the IT Director, Ms. Young was the program director for the National Emergency Medical

Services Information System (NEMSIS) Technical Assistance Center (TAC), where she managed the staff and IT systems to receive, transform, analyze, and report on millions of pre-hospital EMS records. She is a contract Information Systems Security Officer for the federal government and holds expertise in the implementation of Federal Information Security Modernization Act (FISMA) systems. Ms. Young leads a staff of systems administrators, technical support analysts, business intelligence developers, software design engineers, and IT project managers (PM).

Russell Telford, MAS, MA, BA is a Biostatistician and member of the Utah DCC Executive Committee. He has more than 9 years of experience in clinical research and 8 years of experience in education. He currently serves as the Director of Biostatistics and Clinical Data Management. Prior to his current role Mr. Telford was the Biostatistics Manager and a biostatistician providing direct support to clinical research projects. He has expertise with a wide variety of systems and processes related to the Society for Clinical Data Management's Good Clinical Data Management Practice (GCDMP©) and statistical methods. Mr. Telford leads both clinical data management and statistical staff that provide direct support to research projects.

A.2 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.

A.2.1 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.

A.2.2 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.

A.2.3 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.

A.3 Major Software Resources

Extensive software resources are available in the DCC to support its users, including:

- Electronic collaboration using eRoom™
- Electronic data capture systems (Formedix, REDCap)
- 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).

A.3.1 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.

The screenshot shows the eRoom interface for the CPCCRN III Steering Committee and Staff. The left sidebar displays a tree view of the room's structure, including sections like CPCCRN III Steering Committee and Staff, CPCCRN COVID Data.xlsx, and various document and task categories. The main content area is titled "CPCCRN III Steering Committee and Staff" and contains several document thumbnails and links. These include "SharePoint Reports", "Erica Demo_Accessing Consent Documents", "SharePoint Manuscript List", "Meetings", "Subgroups", "Manuscript Documents and Templates", "PI Teleconference Calls", "eBinder 7 min Training", "Contact Information", "Productivity Reports to NIH", "Business Associate Agreements", "Documents for Review", "CPCCRN Slide/Logo Templates", "Family Network Collaborative", "NIH Supplements", "CPCCRN Research Concepts and Studies", "Non-repudiation Letters", "Policy Manual", "Recycle Bin", "CPCCRN COVID Data.xlsx", and "Close-Out Checklists". Below the main content area, there is a section titled "Your Hidden Items" with more document thumbnails. At the bottom, there are buttons for "create", "add file", "mark read", "commands", and a "logout" link. A footer at the very bottom provides information about the 2020 Steering Committee Dates and the Winter Meeting.

Figure 2: Example eRoom™ (CPCCRN Steering Committee eRoom)

A.3.2 Electronic Data Capture Systems

Formedix. Formedix 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. It is desirable to build an

entire study in this platform, and it can be exported to various electronic data capture (EDC) systems such as REDCap, which is described in the next section.

After the study is underway with data collection, Formedix has a dataset conversion feature that allows us to generate Study Data Tabulation Model (SDTM), Standard for Exchange of Nonclinical Data (SEND), and Analysis Data Model (ADaM) submission datasets, based on mapping that was done at the beginning of the study. We can also adjust the mapping. Generation of the SDTM dataset is required if data are submitted for regulatory purposes, and increasingly is a standard for data sharing between clinical studies.

REDCap and MyCap. REDCap is an alternative web-based EDC system that has advantages for collecting patient reported outcomes. MyCap allows creation of phone-based applications that can be used by participants to provide information; this information is then transmitted to the REDCap database. These apps are available for Android and iOS platform devices, and we can use this platform to maintain contact with study participants, facilitating long term retention and follow-up.

A.3.3 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 size of the dataset. 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.

A.3.4 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 use it 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 on the next page). This software provides us 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.

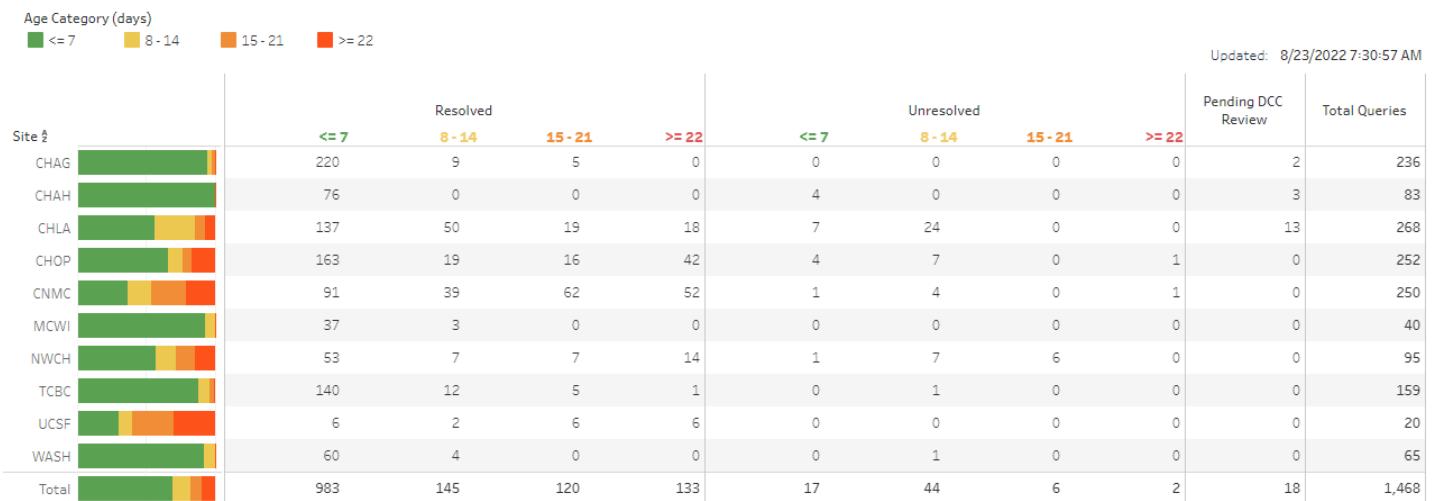


Figure 3: Query system aging dashboard to track queries to resolution

A.3.5 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.

A.3.6 Statistical Software

We use SAS Version 9.4 for most analyses, but also use R for specific reporting purposes. We consider SAS to be most appropriate for conducting trials that are subject to an investigational new drug (IND) application, because SAS has documentation to support its validation, while R is highly customizable by end users.

A.3.7 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 on the following page shows a list of four modules dealing with workflow in one of our previous studies PEACE(AZ); the first module is shown in Figure 4b on the next page. 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.

A.3.8 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 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

This screenshot shows the Moodle course navigation interface for the PEACE(AZ) study. The left sidebar includes links for Home, Site pages, My profile, My courses, and Courses. Under Settings, there are options for Turn editing on, Edit settings, Completion tracking, Users, Filters, Grades, Backup, Restore, Import, Publish, Reset, and Question bank. The main content area displays four course modules:

- Module 1:** PEACE(AZ) Workflow and Database Training. You are expected to have read the protocol prior to reviewing these modules.
- Module 2:** PEACE(AZ) Workflow and Database Training. You are required to view module 1 prior to viewing this module.
- Module 3:** PEACE(AZ) Workflow and Database Training. You are required to view modules 1 and 2 prior to viewing this module.
- Module 4:** PEACE(AZ) Workflow and Database Training. You are required to view modules 1, 2 and 3 prior to viewing this module.

(a) List of Moodle modules for PEACE(AZ) Study

This screenshot shows a Moodle presentation slide for Module 1 of the PEACE(AZ) study. The slide title is "PEACE(AZ) Workflow and Database Training: Module 1". It features a large image of a baby in a hospital setting. The slide content includes the names of the presenters: Stephanie Bisping, BSN, RN, CCRP, and Collaborative Pediatric Critical Care Research Network. The slide also includes a navigation bar with icons for back, forward, and search.

(b) Module 1 presentation

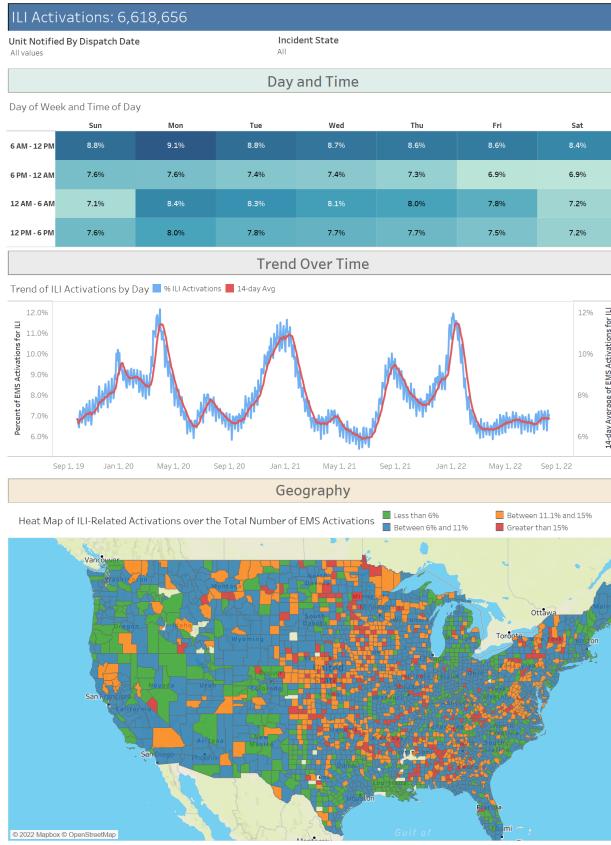
Figure 4: Example online study training with Moodle system.

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 us to maintain strict source control over the protocol and associated documents.

A.3.9 Business Intelligence and Analytics Software

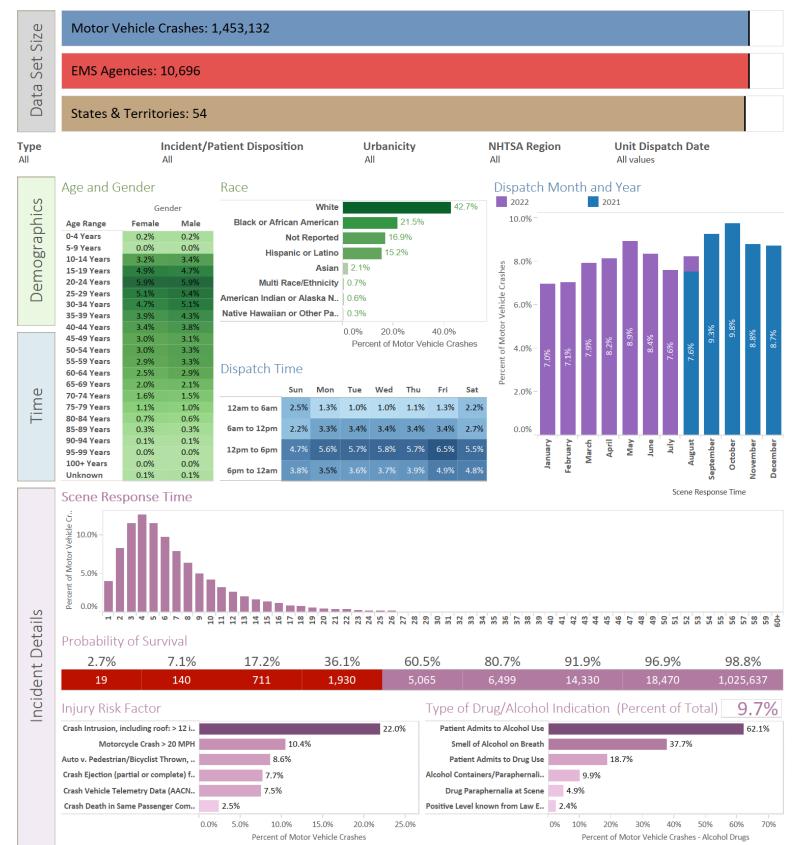
The Utah DCC has extensive experience producing interactive dashboards on our website for public and government partners. An illustrative example from the NEMSIS TAC describes our capabilities. The NEMSIS TAC is hosted at the Utah DCC and facilitates, enables, and promotes the implementation and use 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. As described in section A.3.3, we use 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 on the following page. 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 NEMSIS TAC project, we are able to provide multiple levels of access for the Asian American, Native Hawaiian, and Pacific Islander (AsA-NHPI) Cohort Study, 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.

National Influenza-Like Illness (ILI) Surveillance Dashboard



(a) Example from influenza-like illness

Public V3 Motor Vehicle Crash Dashboard



(b) Example from motor-vehicle crashes

Figure 5: Examples of dashboards designed using Tableau.

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 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 the next page.

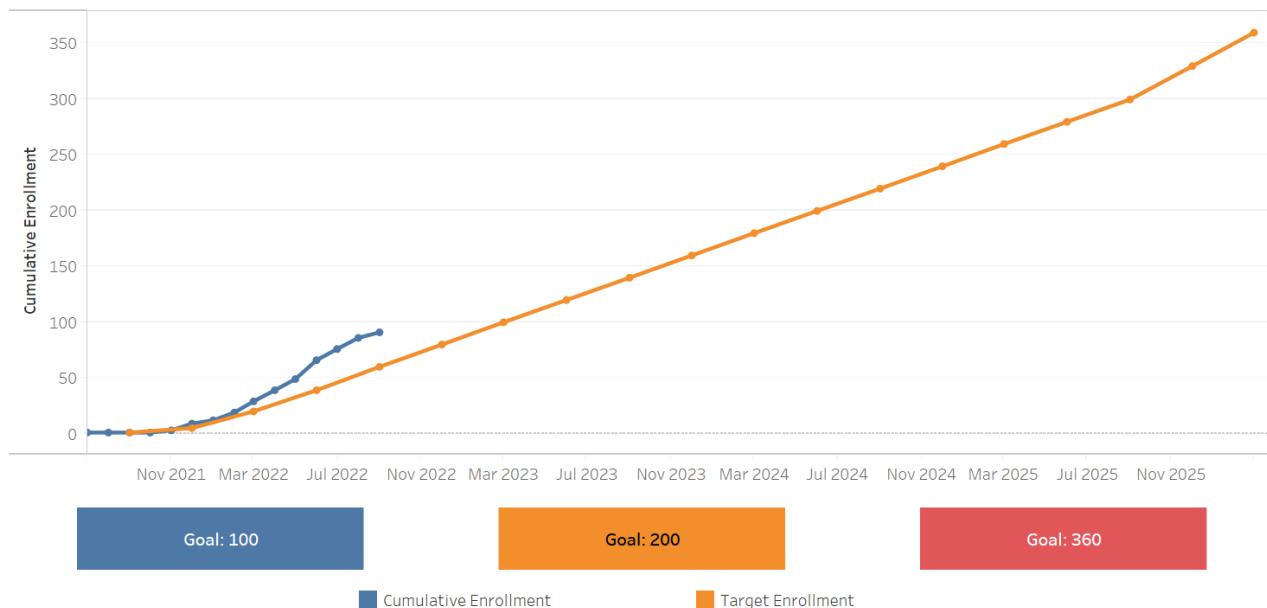
STArT Study Level Enrollment

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.

Figure 6: Sample study enrollment report for the STArT Study in the Utah DCC.

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.

A.3.10 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.

A.4 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©.

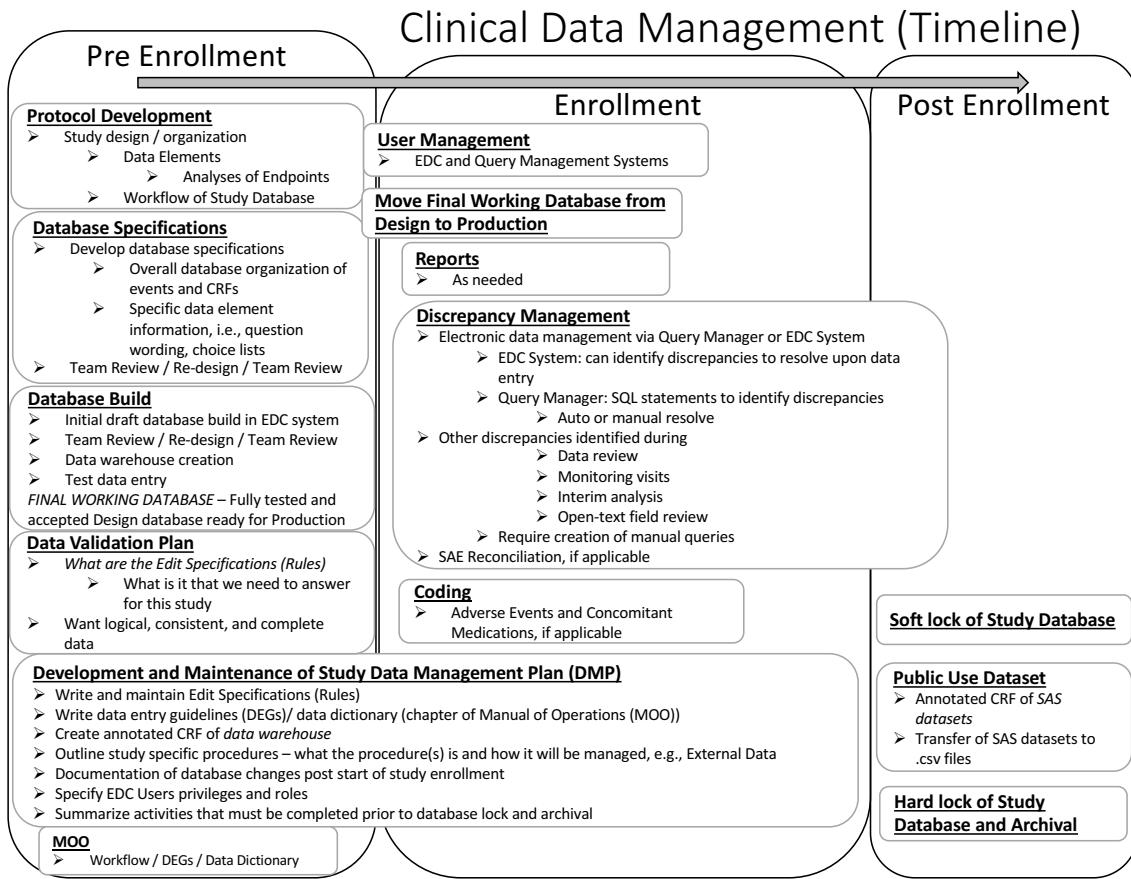


Figure 7: Clinical data management activities across entire study timeline.

A.4.1 Organization and Leadership

Clinical data management is led by Russ Telford, MS who has been a part of the DCC since 2013 as a biostatistician, manager, and now Director of Biostatistics and Clinical Data Management. The DCC has 13 clinical data managers (CDM) with experience in supporting clinical research ranging from industry sponsored work to philanthropic and government-funded studies.

A.4.2 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. This study will obtain granular data regarding participant race and ethnicity (for example, Chinese, Japanese, Samoan, Palauan) and permit multiple race reporting. 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.

A.4.3 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.

A.5 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 on the following page.

BIOSTATISTICS SUPPORT (STUDY TIMELINE)

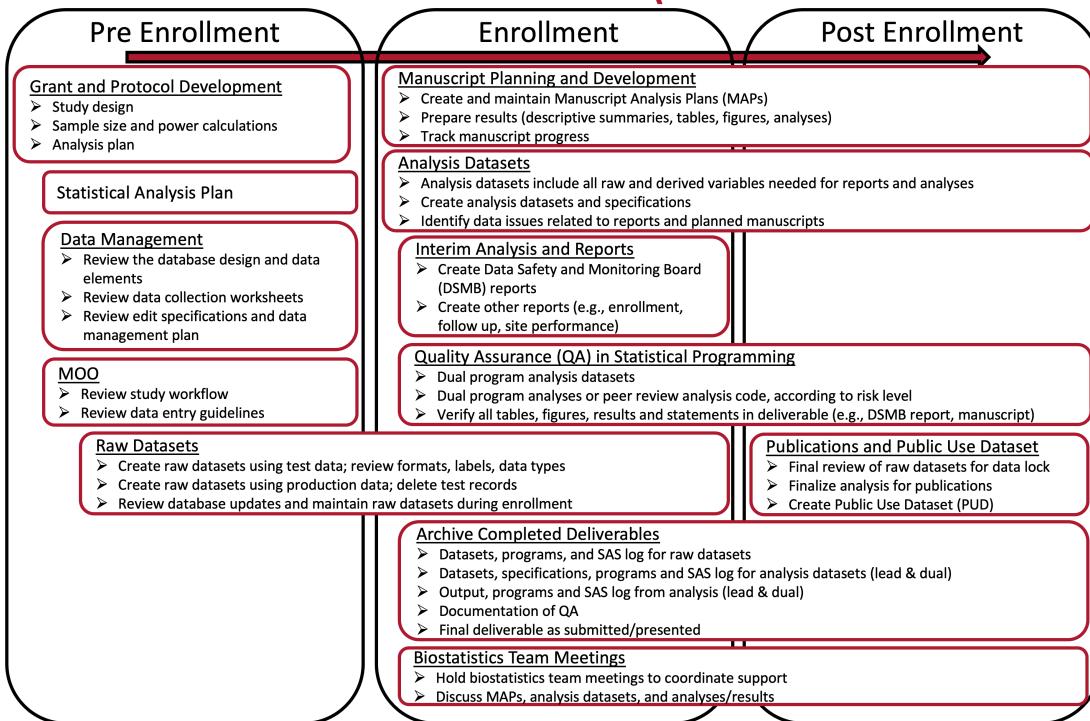


Figure 8: Statistical activities across entire study timeline.

A.5.1 Organization and Leadership

The staff statistical team is led by Russ Telford, MS. The DCC has 21 staff statisticians and 8 PhD faculty statisticians. Each study is assigned a faculty statistician and lead staff statistician. We also assign a second statistician to complete quality control and provide additional statistical support as needed.

A.5.2 Roles Across the Study Timeline

Study Design and Definitions. 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 SAP is written to detail analyses for protocol aims and is a key document in ensuring that correct data are collected.

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 after 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. We will use this experience working with and creating reports for the OSMB set up and reporting.

A.5.3 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.

A.6 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.

A.6.1 Organization and Leadership

The PMP team is supervised by Lisa Young, whose capabilities and expertise are described in Section A.1. 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.

A.6.2 Structure of Study Teams

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 on the next page). 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 on the following page).

A.6.3 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.

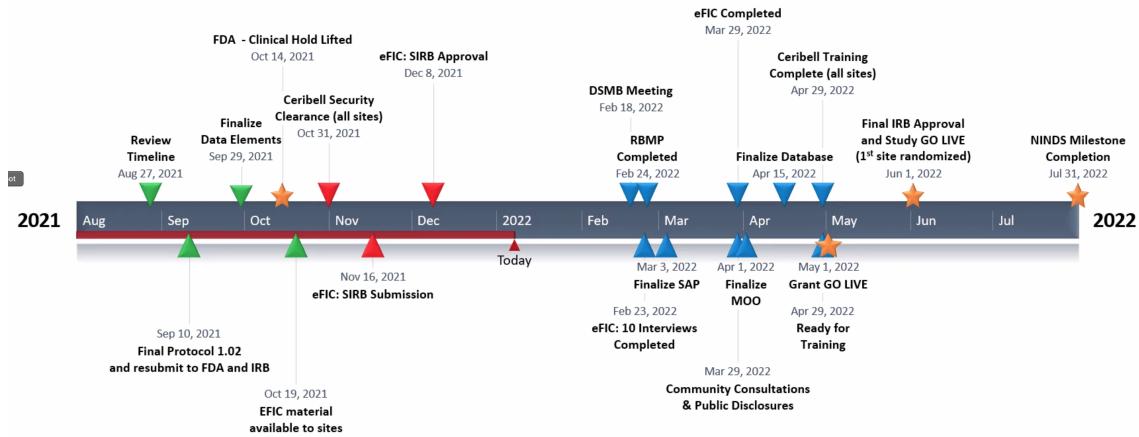


Figure 9: Example study timeline with milestones.

| % 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 | 10 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 | 4755,84 | 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).

A.7 Regulatory Affairs and Quality

A.7.1 Organization and Leadership

The Regulatory Affairs, Compliance, and Quality team is led by Director of Research Amy Goodman, PhD, who directs teammates Maryse Brulotte, Shelly Roalstad, and Marie Kay. 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.

A.7.2 Integration and Support

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, Compliance, and Quality 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, one that enhances the alignment of Regulatory Affairs, Quality, and Standards-adherence. They work closely with study teams providing 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.

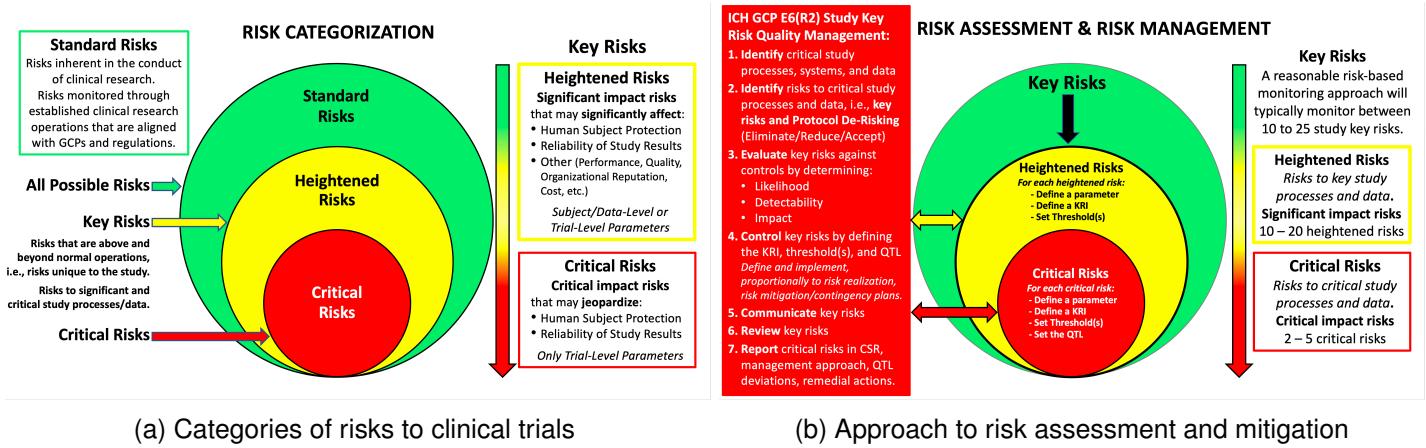
A.7.3 Expertise, Leading Practices, and Collaboration

The University of Utah is a member of the Avoca Quality Consortium (AQC) and participates in Avoca Leadership Advisory Boards that establish best practices for the clinical research industry at large. Avoca has provided the

Utah DCC with access to state-of-the-art practices of over 100 industry members; we are one of the few academic institutions that belong to the AQC.

A.7.4 Risk Management

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). We are abreast of and adapting to ongoing ICH GCP E6, E8 and E3 revisions.



(a) Categories of risks to clinical trials

(b) Approach to risk assessment and mitigation

Figure 11: Conceptual model for risk assessment and mitigation.

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 on the next page 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 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.

A.8 Preparation of Public-Use Datasets

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. De-identification involves randomly generating a new ID for each participant, recoding variables as needed, and

| 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.

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.

A.9 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 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 six additional Standard Operating Procedures relevant to this cohort study:

- 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

A.10 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 CC'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.7.4). 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 DCC offers access to a validated and 21 CFR §11 compliant EDC database for use in FDA-regulated clinical trials.

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

B University of Utah Pacific Islands Studies Initiative

The University of Utah stands apart from other academic institutions due to its strong relationship with Native Hawaiian and Pacific Islander (NHPI) communities. The **Pacific Islands Studies Initiative's (PISI)** at the University of Utah was established in 2016, co-founded by **MPI Kalani L Raphael, MD** and is housed in the School for Cultural and Social Transformation. PISI's mission is to create a vital academic ecosystem, wherein Pacific Islander faculty, staff, students, and community can thrive personally, professionally, and emotionally. The PISI's vision is that the University of Utah will be the premiere academic institution for Pacific Islands scholarship. The

development of the PISI was motivated by two main factors. First, there is a large NHPI presence in Utah and, consequently, the university. According to the 2020 US Census, **Utah ranks third (1.8%) behind Hawai'i (27.1%) and Alaska (2.5%) in terms of proportion of the population that is NHPI**. No other state has a NHPI population that exceeds 1%. Most NHPI in Utah live in two adjacent counties, Salt Lake County (2.5%), which is where the University of Utah resides, and Utah County (2.1%). Hence, the population density of NHPI in the region surrounding the University of Utah is quite high providing an **easily accessible network of community advisors** regarding data standards, integrity, safety, and sovereignty for this project. In addition, to meet the needs of NHPI students, the University of Utah committed financial support to hire five additional NHPI faculty members. The product of this investment was the creation of a Certificate in Pacific Islands Studies that complements any major or minor degree at the university and the Mellon-Pasifika Research Fellows Summer Program. Hence, the University of Utah has a track record of effectively partnering with the NHPI community and an environment that advances NHPI students and communities.

At the center of the PISI is a commitment to recruit and retain Pacific Islander students to the University of Utah through curricular pathways, mentoring, and career planning; encourage Pacific Islands students to engage in critical thought, particularly from an Indigenous Pacific perspective; challenge students to engage in scholarship and research that will create and cultivate knowledge; assist students, faculty, and staff in maintaining strong connections to family, spirituality, and culture; and recruit and retain Pacific Islands studies faculty and staff to the University of Utah through advocacy for faculty and staff development and advancement.

C University of Utah Behavioral Health Innovation and Dissemination Center

The Utah Behavioral Health Innovation and Dissemination Center (BHIDC) at the University of Utah is co-Directed by **Brian Baucom, PhD**, Co-I of this proposal. The BHIDC is a university-wide center that trains graduate students, psychiatry residents, and triple-board psychiatry fellows in evidence-based psychotherapies and creates an interdisciplinary learning environment that spans five colleges within the University of Utah. BHIDC also conducts and supports cutting-edge research focused on developing and testing the efficacy of new psychotherapies and creating resources, such as databanks and text/audio corpora, for interdisciplinary mental health research. Currently, research at BHIDC is supported by federal and international grants and industry gifts. Dr. Baucom is the Director of Research at BHIDC and oversees study design, database creation and maintenance, data curation, and statistical analysis as well as prospective (i.e., inclusion of Common Data Elements) and retrospective (i.e., Integrative Data Analysis)²¹⁰ dataset harmonization for multi-center studies.

D University of Utah Trial Innovation Center

The Utah Trial Innovation Center, or Utah TIC, was funded by the National Center for Advancing Translational Science (NCATS) in July 2016 and is part of the larger Trial Innovation Network (TIN) of the Clinical and Translational Science Award (CTSA) program. **Jamie P Dwyer, MD**, MPI of this proposal, co-directs the Utah TIC with Dr. Dean, and **John VanBuren, PhD**, MPI of this proposal, is a Co-I of the Utah TIC.

The TIN combines three TICs (Utah, Johns Hopkins/Tufts, Duke/Vanderbilt) with one Recruitment Innovation Center (RIC) (Vanderbilt) and approximately 60 existing CTSA Program Hubs, including the Utah CTSI.

The TIN vision is to address critical roadblocks in multi-center trials and to accelerate the translation of novel interventions into life-saving therapies while implementing innovation every step of the way. Operational innovation, operational excellence and collaboration are the network cornerstones.

To achieve the vision of the TIN, the Utah TIC is a multi-disciplinary collaborative effort involving the Utah DCC, IRB, Office of Sponsored Projects, Clinical Trials Office, and the CTSI. Our areas of expertise include project management, data management, biostatistics, contracting, budgeting, regulatory, and research informatics.

We envision that the Utah TIC can support multi-center research projects which are ancillary to the AsA-NHPI Cohort Study, as the study progresses. TIN resources can be requested via a simple online query, and the teams set up an initial intake meeting to understand the project and needs. In particular the RIC may be particularly helpful with specialized recruitment and retention strategies.

E University of Utah Clinical and Translational Science Institute

E.1 Introduction

Jamie P Dwyer, MD, MPI of this proposal, holds key leadership positions within the Utah CTSI, partnering with CTSA Co-PI Dr. Rachel Hess, Associate Vice-President for Research for Health Sciences. CTSI history at the University of Utah dates back nearly eight decades: the (now) Spencer Fox Eccles School of Medicine was established in 1943 with Dr. Maxwell Wintrobe as the inaugural Chair of Internal Medicine. Dr. Wintrobe—a noted hematologist, researcher, and educator—received the first extramural research grant ever awarded by the National Institutes of Health, a translational research project furthering knowledge of muscular dystrophy and other hereditary and metabolic disorders. In 1965, the University of Utah became the second General Clinical Research Center (M01RR00064) in the country. The resulting half-century of continuous funding provided critically important translational capacity for the Intermountain West region and resulted in multiple national and international collaborations. Building on this history of early translational research, the Utah CTSI was founded (and funded by an NIH Clinical and Translational Science Award) in 2008 to provide an infrastructure that promotes new and innovative research programs in clinical and translational science, with official designation as an institute on July 1, 2021.

The CTSI is now the Intermountain West's hub for the development, demonstration, and dissemination of clinical and translational science, with our shared mission to ensure the highest quality clinical and translational science and ultimately improve the health of our population – eliminate health disparities and achieve health equity. In service of this mission, we identify barriers to translational research, develop and test methods to improve research design, conduct, evaluation, dissemination, and implementation. We then deploy methods to support researchers across the translational spectrum—providing community engagement expertise to plan, enhance and support diverse and inclusive recruitment, study design and analysis, informatics, and clinical research infrastructure to the Utah CTSI community. CTSI programs support training of clinicians in research methods and bench researchers in the translational aspects of research.

The CTSI and the Utah DCC collaboratively approach systemic and local barriers in translational science, developing innovative methods or improving more traditional scientific methods via individual translational research projects. Hosted multi-center trials serve as a translational laboratory for testing and demonstrating effective operational improvements to clinical trial processes at University of Utah and across CTSA and other national network partner organizations. SOPs, workflows, clinical research governance to inform guidance or policy (single IRB [SIRB], standard agreements), and informatics-based solutions developed over the last six years are strategically deployed and disseminated.

E.2 Partnerships, Collaborations, and Cores

Institutional partnerships include: CTSI operations and space; Data Science Service; CTSI-managed training grants and post-doctoral Master of Science in Clinical Investigation (MSCI) academic degree program; Inpatient and Outpatient research services infrastructure; CTSI service recharge centers, Regulatory knowledge core including Research Education (REd) courses, support for K12 scholars; K12, T32, R25 mentors; and the Office of Research Participant Advocacy (ORPA) within the Vice President for Research Office of Research Integrity and Compliance.

Office of Research Participant Advocacy. The CTSI's collaboration with ORPA helps to facilitate participant interactions so that they are more efficient, effective, and safer, and provides language access support for non-English-speaking participants through translation and interpretation. ORPA is uniquely structured and acts as the liaison between research participants, researchers, and the IRB. ORPA provides comprehensive translation and interpretation services (providing support for over 27 languages), with a particular focus on comprehension by participants. The office also provides support and education to investigators and their teams on current best practices working with underserved and underrepresented community members, assists with developing recruitment strategies to ensure equitable access and opportunity to research, and provides dedicated research language access services.

Clinical Research Support Office (CRSO) within the CTSI. The Utah CTSI provides expertise and resources

for clinical trials and human participants research spanning T0-T5; the CRSO facilitates operations to support investigators conducting clinical trials and studies in human participants' research. The mission of the CRSO is to train, support or provide a highly skilled workforce, and provide the expertise and tools necessary for regulatory-compliant research conduct, liaising and coordinating with research-essential business units and individual clinical research units across the institution. The CRSO aims to reduce burden and increase efficiencies in clinical research while providing resources, navigation, and knowledge within one central University of Utah office. Cost recovery and growth of our clinical trials portfolio for expanded access to trials in Intermountain West populations are relevant functions. CRSO is the home for informatics tools including OnCore™ Clinical Trials Management System and Epic Research Module, successfully integrated enterprise-wide in Spring 2022.

Community Collaboration & Engagement Team (CCET) within the CTSI. The CCET within the Utah CTSI provides expertise, resources, and support for researchers, individuals, institutions, agencies, patients, providers, and other stakeholders to fruitfully collaborate on projects that address researchers' interests and communities' health needs. CCET provides a menu of services to successfully engage the community in a culturally sensitive way, including engagement sessions, personal interviews, community dialogues, and return of results planning. The CCET recruits participants through word-of-mouth and flyers which are disseminated in clinics, by community organizations, social media outlets, and other locations appropriate to the population being recruited. The flyer contains a QR code that links to a screener survey on REDCap which includes questions to determine eligibility. If the participant meets the entry criteria, the Engagement Coordinator prepares participants by discussing the summary of the research project and the questions that will be asked during the Engagement Session. Participants are encouraged to reflect on the questions prior to the Session and discuss them with other appropriate individuals so they can represent a broad perspective from their community during the discussion. In addition, participants receive a Consent Cover Letter prior to joining the Session; the Engagement Coordinator communicates with them to answer any questions related to the consent process and ensure that participants have reviewed it prior to confirming their participation. Participants are then verbally consented at the beginning of the Engagement Session prior to the discussion being audio recorded. After the Engagement Session, the audio recording is sent by CCET to the research team to be coded and analyzed. The audio recording is saved on a password protected computer.

CCET also provides standardized infrastructure to develop a Community Advisory Board (CAB). CABs build collaborative partnerships between researchers and community members, patients, or other stakeholders. CABs provide a way for researchers to gain input or perspective throughout different phases of a research project such as planning, designing an intervention or tools, recruitment, implementation, data analysis, dissemination, etc. CABs may meet at an interval that is appropriate for the phase of a research project. The experts who participate in CABs are individuals who are members of the population or community that the investigator wishes to involve in a research study. They are experts in their group's culture, history, interests, needs, literacy levels, translation needs, past research and project experiences, and participation supports and barriers. The CCET provides a full CAB service including meeting with the researchers to plan each CAB meeting, an experienced facilitator for the CAB meetings, and an experienced scribe who summarizes the CAB discussion. The study investigators develop the IRB application necessary to constitute the CAB. This type of listening session is typically IRB Exempt Under 45 CFR §46.101(b), Category 2, and as such there is no Continuing Review. The CCET recruits the CAB members, prepares them for each CAB meeting via email and phone calls, and follows up after each meeting. CCET handles all logistics of each meeting, including participant compensation.

Cellular Translational Research Core (CTRC) within the CTSI. The CTRC of the CTSI at the University of Utah provides biorepository, stem cell, and molecular biology services to investigators at the University of Utah. Their mission is to deliver first-class service, up-to-date information, and technical expertise, featuring induced pluripotent stem cell (iPSC) generation and automated nucleic acid isolation, for increased speed, efficiency, and reproducibility. It maintains modern storage infrastructure, data management, and operational guidelines to manage a functional, sustainable, and standardized biorepository model.

F University of Utah Institutional Review Board

F.1 Organization and Leadership

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

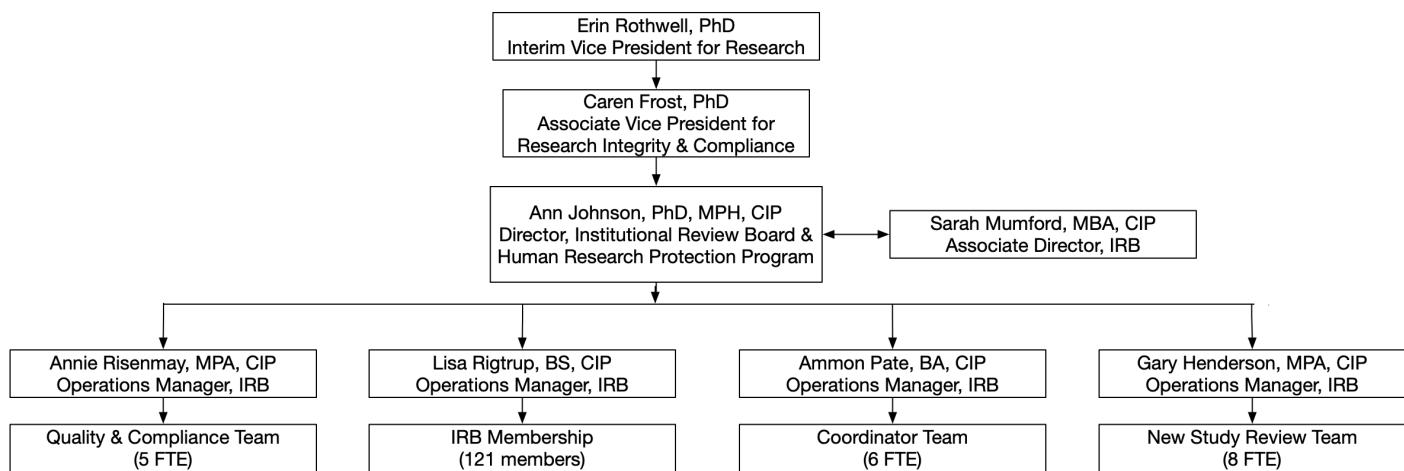


Figure 13: Organizational chart of University of Utah IRB.

Ann Johnson, PhD, MPH, CIP is the Director for the University of Utah Institutional Review Board and Human Research Protection Program, 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 an 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.

F.2 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

F.3 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 900 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.

F.4 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.

Equipment

No equipment is budgeted in this proposal

Biospecimen Plan

The University of Utah intends to be the integrated biospecimen resource for the Asian American (AsA), Native Hawaiian, and Pacific Islander (NHPI) Cohort Study, via a dedicated biorepository and central laboratory. The Cellular Translational Research Core (CTRC) of the Clinical and Translational Science Institute (CTSI) at the University of Utah is proposed to serve as the dedicated biorepository, and Associated Regional and University Pathologists, Inc. (ARUP) Laboratories, located on the campus of the University of Utah, is proposed to serve as the central laboratory. Among many features, the CTRC provides biorepository services to investigators at Utah. It maintains modern storage infrastructure, data management, and operational guidelines to manage a functional, sustainable, and standardized biorepository. ARUP is a diagnostic and national reference laboratory that also serves as the primary laboratory for the University of Utah Hospital and Health System clinics. ARUP has a strong scientific mission and conducts diagnostic tests for clinical research projects. ARUP maintains operations 24/7/365, and with its central location across the contiguous states, Alaska, and Hawai'i, ARUP is optimally suited to function as the central laboratory for the AsA-NHPI Cohort Study.

A Activities and Plans to Support an Integrated Biorepository and Central Laboratory Resource

We reviewed the currently conducted NHLBI cohort studies and identified commonly measured cardiovascular risk factors to inform our proposed set of tests to be conducted at the central laboratory (ARUP). Although the final set of tests will be determined during the UG3 phase, we have budgeted for the following measurements (Table 1) to be performed by the central laboratory at the Baseline Exam (BL), and at the Year 2 Exam (Y2):

| Test Name | ARUP Lab Code |
|---|---------------|
| Complete metabolic profile (CMP) | 0020408 |
| Complete blood count (CBC) | 0040003 |
| Hemoglobin A1c | 0070426 |
| Albumin:creatinine ratio, urine | 0050203 |
| Lipid panel, extended | 0020468 |
| Troponin T, cardiac, 5 th generation | 3001831 |
| Uric acid, serum | 0020026 |
| Lipoprotein a | 0099174 |
| Homocysteine, total | 0099869 |
| C-reactive protein, high-sensitive | 0050182 |

Table 1: Proposed tests to be performed by the central laboratory at the Baseline Exam and Year 2 Exam

Our biospecimen storage plan was developed in consultation with the CTRC Director and considers the minimum number ($n = 10$) of ultralow freezers that can be comfortably committed to this cohort study, described in more detail below. We have budgeted for the following biospecimens to be collected at the CCFCs at the BL visit and at the Y2 visit (note: we do not propose to collect DNA and RNA at the Y2 visit) and shipped to the Utah biorepository for processing and storage:

| Specimen | Volume or Weight | Number of Tubes |
|-----------------------------------|------------------|-----------------|
| Serum | 0.25mL | 4 |
| | 1mL | 4 |
| Plasma | 0.25mL | 4 |
| | 1mL | 3 |
| Urine, random (spot) | 1mL | 5 |
| RNA, PAXgene, whole blood | 2.5mL | 1 |
| DNA genomic, PAXgene, whole blood | 2.5mL | 1 |
| Nail clippings, toe | 100mg | 2 |

Table 2: Proposed biospecimens to be collected and shipped to the biorepository

B CTRC Capabilities to Operate and Manage a Biorepository

The CTRC at the University of Utah is a multi-function translational laboratory resource for University of Utah investigators and external collaborators. Specific expertise areas of the CTRC include stem cell services, DNA and RNA extraction services, and biorepository services. Of relevance to the AsA-NHPI Cohort Study are the CTRC biorepository services and, potentially, DNA and RNA extraction services.

The CTRC has stored cryopreserved biospecimens, including storage in liquid nitrogen, for decades. The CTRC provides affordable cryostorage rates for investigators while maintaining high integrity specimen management using the OpenSpecimen platform. The CTRC routinely processes and aliquots blood and urine samples, which we anticipate will be collected in this study, for long-term storage and can store other specimen types as well (toenails, saliva, hair). Freezers are connected to emergency power sources, temperature is monitored 24/7/365 to identify deviances, and protocols are in place to manage temperature deviances and freezer failures should they occur. The CTRC uses a phone-based system called Sensaphone to notify CTRC biorepository staff of any temperature deviances. The advantage of a phone-based system is that if power goes down completely, including emergency power, phone lines can send out an alarm to CTRC mobile phones. To provide investigators with an option for real-time monitoring, the CTRC is exploring the addition of a second, ethernet-base monitoring system.

As mentioned above, the CTRC has the capacity to comfortably commit ten -80 °C freezers to the AsA-NHPI Cohort Study. This is a conservative estimate that considers the CTRC's responsibility to store samples for other investigators as well, and more freezers could be available depending on future demand. Considering that many -80 °C freezers hold 600 standard size cryoboxes, the CTRC will be able to store a minimum of 6000 cryoboxes (486,000 1.5mL cryotubes) in this study. Based on our proposed sample storage plan in Table 2, each participant will have 22 (plasma, serum, urine, toenail) 1.5 mL tubes stored at each visit (440,000 total, 5432 cryoboxes if there are no missing samples). The remaining space would be used to store the 20,000 2.5 mL PAXgene tubes (DNA + RNA) collected at baseline.

Collection and specimen processing protocols will be designed to meet the specific requirements of the protocol and future ancillary studies. In the AsA-NHPI Cohort Study, specimen collection will be managed by coordinators at the CCFCs. The Utah CC will provide bar-coded labels with the participant's unique ID to the coordinators to place on specimen containers. Specimens will then be shipped overnight to the Utah biorepository for processing, aliquoting, and storage. Each tube in the biorepository will have a bar-coded, cryogenic-freezer label with the participant's unique ID and a separate OpenSpecimen number to identify each tube and its contents (e.g., serum, plasma, urine). The OpenSpecimen number will be entered into the cohort study database managed by the CC to link the specimen to the participant. We have also budgeted for specimen returns where leftover samples from the central laboratory (ARUP) are transported to the biorepository for storage. These samples will be coded similarly but include special notation in OpenSpecimen to indicate that it is a residual sample from the central laboratory.

The Utah CTSI supports the use of OpenSpecimen for management of research biospecimens at the CTRC. OpenSpecimen is an open-source application and database providing researchers a simplified process of recording location and metadata associated with specimens used in clinical and translational research. OpenSpecimen is a multi-tenant system that manages protocols with role-based, HIPAA-compliant permissions and utilizes standard vocabularies to record specimen-based data fields. Capturing data using standards compliant values ensures that the searching and export of data across protocols in the system can be used in a harmonized fashion. A Common Security Model is used to support authentication, authorization, roles, and privileges. A major feature of OpenSpecimen is that samples can be quickly located and retrieved with this platform. OpenSpecimen supports a "specimen catalog" interface that can be used to query for available samples across all future protocols that may be developed for the AsA-NHPI Cohort Study.

Upon completion and final closure of the AsA-NHPI Cohort Study, the CC will assign new study numbers for all participants and codes to identify each tube in the biorepository and its contents. The CC will then instruct the biorepository to strip all samples of their original study identifiers and re-label them with the new study labels. This will prevent investigators from using the original study identifiers to identify individual participants in the future.

These de-identified linked data and specimens will then be submitted to NIH repositories.

The CTRC also has the technical skill to extract high quality DNA and RNA from blood and any conceivable tissue type should these be included in the main protocol or a future ancillary study. The CTRC offers manual or automated DNA and RNA extraction and determines nucleic acid sample quality and quantity using a variety of approaches including spectrophotometry, fluorometric quantitation, and standard or automated gel electrophoresis, as appropriate.

The CTRC follows all University of Utah, State, and Federal guidelines. Human samples processed by the CTRC have approved IRB numbers and all samples in the biorepository are de-identified. The CTRC does not interact with any participants, it only processes human samples and tissues. University of Utah's Institutional Biosafety Committee tracks laboratory staff training and manages audits of laboratory spaces. The Environmental Health and Safety Administrative Management System provides complete safety compliance guidance for all personnel, to recommend up-to-date safety protocols and to maintain compliance with all regulations.

C ARUP Capabilities to Operate and Manage a Central Laboratory

ARUP is a nonprofit, academic organization of the Department of Pathology at the University of Utah in Salt Lake City, UT. ARUP is a national reference laboratory and primary laboratory for the University of Utah Hospital and Health System clinics. ARUP has an active research mission through the ARUP Institute for Clinical and Experimental Pathology. The institute has four project categories: creating new laboratory tests, improving current clinical laboratory tests, evaluating and critiquing existing laboratory tests, and conducting clinical research projects. Of relevance to this cohort study is ARUP's experience conducting laboratory tests for clinical research in its Clinical Trials sector. The Clinical Trials sector has worked with a variety of investigator types including clinical research organizations, pharmaceutical companies, local investigators, and biotechnology companies.

ARUP is one of the most automated laboratories in the U.S. Most automated capabilities are unique to ARUP, existing nowhere else in the world. This automation is a direct result of a team of engineers, software developers, and managers who have developed the automation process. The main automated transport and sorting system has several components:

1. A chain conveyor system that transports tubes from Specimen Processing workstations
2. Interface robotic systems (binders) that read the tube barcodes and transfer the tubes from specimen transport carriers to pucks
3. The main MagneMotion automated transport system
4. Automated camera systems that use optical character recognition technology systems to identify mislabeled specimens
5. Thawing & mixing workcells
6. High-speed automated sorters.

Specimen collection protocols will be designed to meet the specific requirements of the protocol and future ancillary studies. To optimize specimen integrity, ARUP will provide the supplies (as kits) necessary to CCFCs to facilitate proper collection, transfer, and transport. The Utah CC will provide bar-coded labels with the participant's unique ID to the CCFC research coordinator to place on each specimen container. A representative from a contract courier in the CCFC's service area will pick up specimens from the CCFC and transport them overnight to ARUP. Shipments to ARUP arrive continuously, ensuring rapid turnaround times on results. Throughout the transportation process, the Logistics and Transportation Department employs a variety of quality assurance indicators that monitor and assure specimen integrity. ARUP continuously monitors the shipping regulations of medical specimens established by the International Air Transport Association (IATA) and Department of Transportation (DOT) to remain in compliance.

Apart from its expertise in clinical diagnostic testing and integration with the University of Utah, ARUP is in Salt Lake City, UT, and is ideally situated to receive samples from across the U.S., including Alaska and Hawai'i. The Salt Lake City International Airport is a major transportation hub and one of the fastest growing airports in the U.S. Hundreds of flights enter Salt Lake City daily, including direct flights from Honolulu (O'ahu) and Kahului (Maui).

D Adherence to Good Laboratory Practice

D.1 Biorepository

The CTRC adheres to 21 CFR §58 (Good Laboratory Practice for Nonclinical Laboratory Studies) as well as other parts of 21 CFR as appropriate for clinical investigations regulated by the U.S. Food and Drug Administration (FDA). CTRC applies the principles of the Organisation for Economic Co-operation and Development's (OECD) Good Laboratory Practices (GLP) to nonclinical laboratory studies, as adopted by the FDA and insofar as the standards and requirements are consistent with 21 CFR.

OpenSpecimen adheres to the operational concerns for GLP related to the OECD standard “Application of GLP Principles to Computerised Systems”.²¹¹ OpenSpecimen meets the validation requirements for 21 CFR §58 related to data management for specimen receipt, processing, location management, retrieval, and retention of sample linkage to participant and collection time points.

The Utah CTSI has implemented OpenSpecimen in a HIPAA-compliant protected environment housed within the Center for High Performance Computing (CHPC) at the University of Utah Downtown Data Center. In support of GLP, the OpenSpecimen environment addresses the following areas of GLP concern: accuracy checks; role-based data access and storage of data; audit trails; change management and configuration management; periodic review; physical and logical security, data integrity; data approval; archiving, and business continuity and disaster recovery. Additional factors supporting GLP include:

1. All workflows are implemented in a “draft-mode” for validation prior to actual implementation for any protocol or protocol changes.
2. There is an audit trail of all changes to all workflows and all recorded data within a protocol.
3. There are both manual and automated reporting functionality for all data fields customizable reporting needs.
4. Quality assurance fields are included to track freeze/thaw cycles of specimens, all transfer events, and any processing event associated with the specimen.
5. Container maintenance tasks can be created to schedule, track, and set reminders to perform any maintenance activity performed on any storage containers (e.g., de-icing, monitoring temperatures).
6. The biospecimen catalog meets the requirements for public transparency of the availability of the deidentified specimen collection.
7. Specimen request management is via a catalog feature. All requests go through an approval process and specimen distribution can be tied to consent statements at the participant level. All distribution details, such as investigator, addresses, IRB, or materials transfer agreements are tied to each distribution protocol. Samples can be reserved to specific distribution protocols to ensure their availability to any prearranged collaborators. All orders are maintained in the system for retrieval at any time.
8. Specimen queries and shipping manifests can be designed to meet the requirements of any distribution protocol.

The security audit conducted by Johanson LLP affirms that OpenSpecimen’s information security practices, policies, procedures, and operations meet the Service Organization Control 2 (SOC 2) standards for security, availability, and confidentiality.

D.2 Central Laboratory

ARUP is a CAP-, ISO 15189-, and CLIA-certified laboratory, and holds current licensure or permits required by state or local regulations. ARUP is compliant to GLP as applicable to the clinical laboratory services provided. Abidance to ISO 15189, CAP and CLIA ensures ARUP has the applicable framework in place to provide quality laboratory testing services. This framework includes the following areas:

- qualified personnel
- environmentally controlled facilities, with proper safety measures in place
- validated test systems and equipment
- maintenance of equipment

- quality monitoring of test systems
- validated computer systems
- document control
- management review
- internal audits
- inventory control
- vendor management/purchasing controls

E Oversight of Biospecimens

Oversight of the biospecimens is managed by the Biospecimen Committee, in conjunction with the project managers assigned by ARUP and CTRC. The Biospecimen Committee is fully described in *Overall Structure of the Study Team*.

Cohort Management Plan

A Organizational Structure of the AsA-NHPI Cohort Study

The Utah DCC has successfully coordinated and managed multiple networks and has established collaborative organizational structures for these networks. The **Steering Committee** (SC) will be composed of CC MPIs, the CCFCs PIs, and NIH Program Office staff, as described in Section B of *Overall Structure of the Study Team*. The SC will designate committees to carry out specific network functions. These committees are advisory to the SC. Additional committees may be established at the discretion of the SC, and committees may be dissolved if their primary purpose has been completed. Working groups are coalitions of interested investigators and staff aligned for a cross-committee purpose, or a time-limited deliverable. We note that committee members may be Co-Investigators at the sites and might not always reflect the CC or CCFC contact PI. Visually, an overview of the network can be seen in Figure 1.

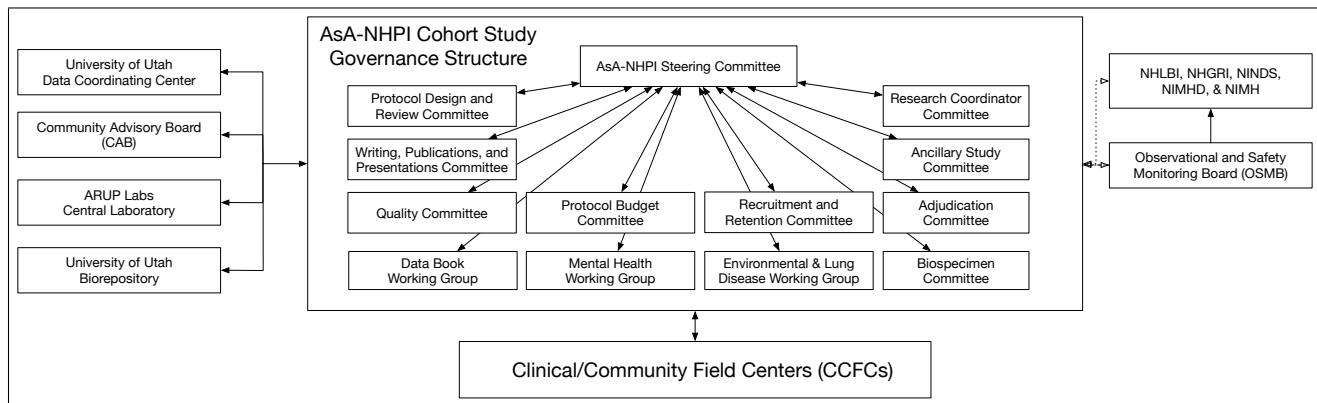


Figure 1: AsA-NHPI Cohort Study Organizational Chart

While the SC will finalize the list of committees and memberships during startup, we briefly describe our proposed committees that we have successfully implemented in our other managed networks. An overview is included in the bullet points below and we then provide further details in *Overall Structure of the Study Team*.

The first priority of the established committees will be the creation and implementation of the AsA-NHPI Cohort Study during the UG3 phase followed by the UH3 phase, and they will then continue their duties when ancillary projects are proposed and funded.

- Protocol Review and Design Committee - reviews protocols to provide feedback to investigators.
- Protocol Budget Committee - reviews protocols for budget feasibility.
- Recruitment and Retention Committee - monitors and develops materials to aid recruitment and retention.
- Research Coordinator Committee - protocol development/implementation and review of progress and issues.
- Quality Committee - reviews site performance metrics and assists CC with risk-based site monitoring.
- Writing, Publications, and Presentations Committee - reviews proposals/manuscripts prior to submission.
- Adjudication Committee - adjudicates outcome variables based on domain area expertise.
- Ancillary Science Committee - solicits and reviews proposals for novel analyses, studies, or interventional trials to be implemented in the network.
- Biospecimen Committee - reviews protocols for central lab and biorepository needs.
- Community Advisory Board - advises the CC on study materials and conduct.
- Data Book Working Group - advises the CC on the design of and content for the data book.
- Mental Health Working Group - dedicated to the safe collection and maintenance of the mental health instruments and outcome assessments.
- Environmental & Lung Disease Working Group - dedicated to issues regarding environmental factors, particularly as they impact lung disease.
- Ad hoc committees or working groups for time-limited purposes, such as in response to urgent public health or societal threats.

A.1 Creation of Study Materials

The CC will work with the CCFCs to finalize the trial protocol during the UG3 phase of the funding period. Our Project Managers (PM) will lead the Risk Assessment and Risk Management process and will work with the sites to identify workflow practices at each site that could impact protocol compliance. These findings will be integrated into the protocol to avoid deviations and assure consistent processes. Identification of risks to data integrity will also occur, and the CC PM will assure that these aspects are built into the database to help clarify data entry requirements and create appropriate data queries. Once the content is finalized and approved by the SC and the OSMB, we will produce the finalized protocol for IRB submission. **We anticipate the University of Utah's IRB will act as the single IRB for the AsA-NHPI Cohort Study.** The CC will incorporate specific aspects of the protocol into the study Manual of Operations and assure consistency across these two key documents. The data entry systems, communication mechanisms and training will be delivered with appropriate focus on study-specific details and focusing on risks to data entry and avoiding areas at risk for noncompliance in the protocol.

B Training & Monitoring of Study Sites & Staff

As is evident from our collaborations described in the *Facilities and Other Resources* section, the DCC has extensive experience in comprehensively supporting multi-center research protocols from conception to implementation. In this section, we describe how we utilize risk assessment and risk management to drive training and monitoring of sites.

B.1 Quality Management and Risk Assessment

The Utah DCC has devised a quality management system and a risk-based assessment approach based on the International Council on Harmonization (ICH) Good Clinical Practice (GCP) E6 R2 guidelines. We will collaborate with investigators during protocol development to identify areas of potential risk to participant safety, data integrity, and regulatory compliance (instead of performing risk assessment *after* the protocol has already been developed). This allows us to revise the study protocol to help assure adherence and minimize risk of threats to the study. We have led this “risk-based study management” effort in over 30 recent studies, and formally trained study investigators and coordinators on this approach. In addition, as a best practice, we evaluate the risk of conducting the study at sites after the protocol is finalized to identify complex procedures and variance from clinical standard of care or processes that may impact participant safety. We produce a written risk assessment document and develop training, reporting, and monitoring plans to address processes or data at high or moderate risk. Finally, we provide the risk assessment document to sites and ask investigators and coordinators to evaluate risks in the context of their own study flow and develop site-specific procedures as needed.

These risk activities provide a solid and innovative methodology to conduct studies that produce high quality data and protect human participants. As an example, in a recent clinical trial of four fluid resuscitation arms, we produced site-specific graphs of expected vs. actual fluid totals. As fluid volumes were controlled by multiple people in different units, this was an area of risk for accidental noncompliance. These reports were updated nightly so that over or under fluid replacement could be identified immediately. Sites with substandard compliance were required to identify root causes for the non-compliance and provide a written improvement plan. Data were subsequently monitored to assure improved adherence, which was achieved in the trial. We will implement a similar innovative approach to assess overall and site-specific compliance in the AsA-NHPI Cohort Study.

B.2 Lessons Learned Regarding Training and Monitoring

Our overall experience with training and monitoring has reinforced several critical lessons that guide our approach to managing potentially complex multi-center clinical studies:

- Study-specific, risk-based training is essential to the successful implementation of a study.
- Clinical investigators and research coordinators require frequent retraining about GCP, regulations, and other aspects of multi-center research.
- Centralized yet collaborative development of final protocol documents, data collection instruments, and the Manual of Operations is important for efficient study implementation.

- Studies require site monitoring to assure protocol adherence, regulatory compliance, and high-quality data. While physical site monitoring is beneficial, it is important to supplement with remote monitoring.
- Analysis of data queries enables early identification of misunderstood concepts or ill-defined data elements, and ongoing training about data quality is needed throughout every study.
- Performance of clinical sites has been improved and maintained by publishing site metrics for all investigators and coordinators to view.
- Implementing risk assessment processes that are specific to the study makes efficient use of resources and prioritizes quality initiatives during the study. Monitoring, data queries, and training should all focus on data critical to the outcomes.
- It is critical to maintain energetic engagement of sites and investigators to avoid “study fatigue”. Regular training should be incorporated to help maintain energy.
- Providing useful feedback on performance yet avoiding query overload helps maintain site performance.

B.3 Training

The CC will plan all study training methods. We use innovative training approaches for initial training, re-training (for staff turnover), and competency-based training. Prior to study start, we use the risk assessment process to identify critical study areas. We structure a large portion of the training sessions to focus on aspects of the trial critical to participant safety, data accuracy, and trial integrity. To avoid training fatigue and ensure understanding of procedures, we may offer “hands-on” practice sessions to prepare research coordinators for high or moderate risk areas. For example, if certain eligibility criteria are relatively complex to evaluate or enter into the data system, we will conduct a mock review during training to help clarify the determination of eligibility. These types of active sessions provide an interactive, engaging training environment. For the AsA-NHPI Cohort Study, we will conduct extensive in-person and remote training sessions for clinical staff and investigators at each site prior to study initiation. New site staff on-boarded after this time will receive training from the local CCFC in addition to requiring successful completion of online trainings prior to joining the study. Based on our previous experience, the number of data queries, emails, and telephone calls from CCFCs to the CC will be inversely related to the investment in training of staff at the clinical sites.

B.4 Site Monitoring

Typically, the Utah DCC uses a combination of on-site monitoring and remote monitoring. We match the risks of the study, as identified in a study risk assessment document, to the most suitable and efficient monitoring approach. For items difficult to detect centrally (e.g., failure to report clinical outcomes such as stroke or MI), we rely on in-person and remote source document monitoring visits (described below). Monitoring efforts are focused on procedures and data with a higher risk profile. Data management, statistical, and project management plans will be developed and updated as needed in an overall Monitoring Plan. The comprehensive data management plan includes discrepancy rules, which fire when data errors or omissions are detected. Our business analyst team will collaborate with our biostatistical team to generate meaningful reports that identify specific performance metrics. When performance thresholds are reached, we follow the steps outlined in the Monitoring Plan.

The monitors, when travelling to do in-person site visits at the CCFC, will follow a specific plan to conduct the visit. The purpose of the visit is to review study procedures, conduct a walk-through of the participant flow, review eligibility processes and criteria, review consent/assent procedures, and instruct investigators and staff on their roles in the study. The monitor will also perform source data verification by comparing data from the Electronic Health Record (EHR) to the database. Finally, the monitor will verify adherence to the study protocol and will review regulatory compliance at each site. Monitoring reports will be shared with the CC prior to being sent to the CCFCs for review by the CC investigative team.

We will supplement in-person monitoring with remote monitoring. Remote monitoring will be achieved by review of specific source documents (uploaded to our Electronic Data Capture ([EDC] tool, typically Florence eBinder) or by gaining access to the site’s EHR for review of clinical data. As both methods have proven successful in particular settings, we will outline the exact approach for the AsA-NHPI Cohort Study in our Monitoring Plan. Procedures performed during remote monitoring visits are similar to those for in-person visits.

C Data Harmonization and Common Data Elements

The AsA-NHPI Cohort Study will systematically collect high-quality data. Standardized assessments are supported by harmonization across sites and instruments. This process ensures the collection and analysis of characteristics that are clearly defined, consistently used, and transparently presented. Common Data Elements (CDE) provide structured human- and machine-readable definitions of study data elements. The use of CDEs supports sharing of study-generated data and results, enabling the resources to be searched, analyzed, and used to make new discoveries based on FAIR (findable, accessible, interoperable, and reusable) data principles.²¹²

The CC, CCFCs, NHLBI and collaborating Institutes will include the use of CDEs and measures across the development of the AsA-NHPI Cohort Study protocol. The CC will facilitate review by the NHLBI-appointed OSMB and approval by the NHLBI and collaborating Institutes. Such harmonization is normal practice for the Utah DCC. During protocol development, we harmonize data elements and data collection forms, converging on a set of core (required) and supplemental (optional, or only collected at some sites) items, keeping in mind the potential high value in datasets that can be used for meta-analyses or other future studies, balanced with concerns such as respondent burden and cultural appropriateness. We identify which questionnaires and assessment instruments are validated (and which are modified or locally developed) and help sites obtain permissions for use of copyrighted materials. Utah DCC informatics faculty partner with data managers and biostatistical faculty to facilitate linking of study databases to CDEs to verify that summary scores and analytics correspond with validated metrics.

Our team is uniquely qualified to support this work. We have long-standing experience developing and documenting standardized data. Our informatics team has been instrumental in the documentation and implementation of CDEs across the NIH Helping to End Addiction Long-term (HEAL) Initiative.^{150,213} Co-I Dr. Sward leads HEAL-wide harmonization and data sharing efforts,¹²⁴ working closely with NIH Program Officer Dr. Wandner and other NIH leaders, site investigators and staff, and the HEAL data ecosystem team to define and document data, implement and utilize CDEs, and to develop metadata that will enable functionality of the HEAL data ecosystem. We have already documented and mapped many of the expected core metrics for the study (demographic measures such as age and sex at birth, WHODAS, PHQ-9, GAD-7). We plan to preemptively document the CDE for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). We recognize that some standard demographics (e.g., race and ethnicity) CDEs will need to be revised to appropriately reflect the population enrolled.

Using a similar process of metadata generation as were employed for other CDE projects,²¹⁴ products include identification of standardized data elements; data specifications for each element—definition, allowable responses, and response format (coded, numeric, multiple choice, free text); and 508-compliant template study forms²¹⁵ to support accessibility documents for persons with disabilities. Biostatistics faculty typically prepare enhanced documentation for key instruments detailing instrument validation, subscale coding, and similar procedures that enhance the rigor and reproducibility of analyses; and include such metadata in documentation for public-use datasets. We are familiar with nontraditional data including environmental data, social determinants, and data from digital health tools.²¹⁶ Team members have supported the documentation of non-English-language versions of several instruments, and we have planned to develop any necessary translations for this cohort study.

We map study elements to extant published CDEs (and other relevant standards) and submit new elements for publication. **We are currently collaborating with National Library of Medicine (NLM) staff to format HEAL CDE files for submission to the NLM CDE repository.**²¹⁷

D Data Collection Methods

The Utah DCC supports multiple methods for the collection of clinical data, including manual chart abstraction and data entry into a 21 CFR §11 validated REDCap database. In some cases, sites are restricted to their internal network, which precludes them from accessing the Utah DCC hosted database. In this situation, the clinical data manager exports the finalized data dictionary. The data dictionary contains the metadata and structure used to construct an identical database. The site imports the data dictionary into their local instance of REDCap and

subsequently enters participant data into their local database. To exchange data between systems, either as an import, export, or both, the two instances will connect via the REDCap Application Programming Interface (API). The Utah DCC's REDCap environment, including API data flow, is depicted in Figure 2. This secure transmission of data uses tokens as a means of authenticating and validating all API requests that are received. In all scenarios for collecting and storing clinical data, the Utah DCC implements encryption in-transit and at-rest.

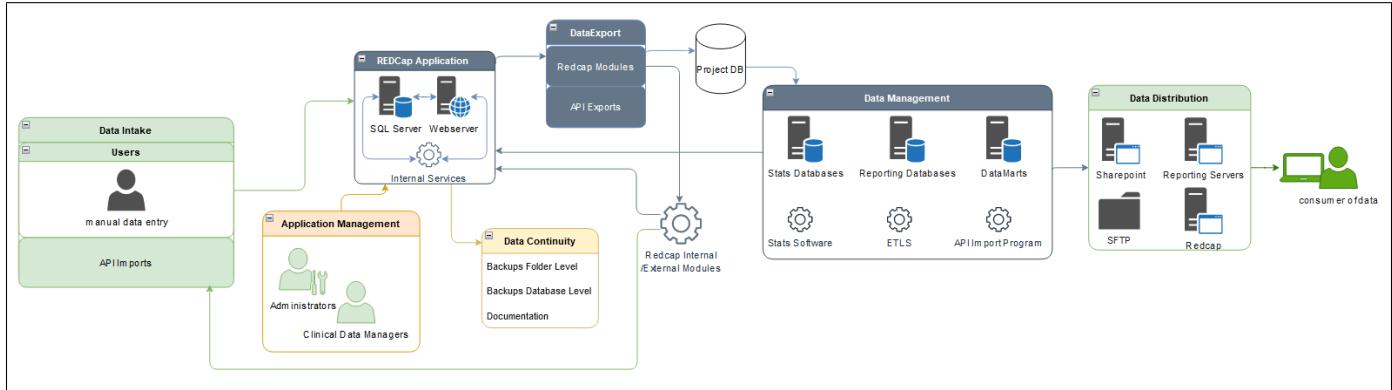


Figure 2: The Utah DCC REDCap environment, including API data flow, to enable EHR to EDC data transfer.

Although data elements collected across all sites and participants will be the same, it is critical that sites have the flexibility to customize data submissions methods to meet their needs. We recognize and appreciate some sites may not have the necessary IT infrastructure to set up this process of automatic data collection, some data elements might not be accessible through the EHR, and some information might be collected directly from the participant. For this reason, we will offer the full spectrum of data collection methods, from 100% manual data entry to complete automatic data transfer, that each CCFC can customize to suit their needs and the needs of their partnering organizations. We have budgeted such that we can support minor improvements in a site's IT infrastructure should they wish to utilize automatic data transfer.

D.1 Innovative Approaches to Data Collection

Data collection by manual chart abstraction on 10,000 participants is laborious and prone to data entry errors. EHR to EDC integration reduces the burden of manual data entry and increases the accuracy of the data. Integration involves the use of an industry-standard operability model, such as Fast Healthcare Interoperability Resources (FHIR) or Health Level Seven (HL7) to automatically extract desired data elements from the study site's EHR to the EDC. FHIR defines how healthcare information can be exchanged between different systems by implementing RESTful web services and open web technologies, such as JavaScript Object Notation (JSON). RESTful web services are the basis for data exchange. We have extensive experience in the design, development, and implementation of RESTful web services to operationalize the collection of data. As an example, the Utah DCC hosts the Pediatric Emergency Care Applied Research Network (PECARN) Registry, a harmonized clinical registry that includes data from multiple sites and EHR systems. The selected data elements are auto-extracted from each site's EHR in a format that conforms to a common data model, deidentified, validated against an XML Schema Definition (XSD), and securely submitted to a central data warehouse at the Utah DCC. The ability to automate the export of EHR data to the EDC will depend on the readiness of each site. Utah DCC possesses robust IT capabilities and will support individual sites' technical needs.

D.2 Digital Health

Technology in health research has rapidly transformed in the past decade. With the advancement of direct database-to-participant communications such as photo uploads and texting, wearables, and sensors (collectively we refer to these as Digital Health), participant data can now be collected directly. We have the existing capability to utilize Digital Health tools in the AsA-NHPI Cohort Study to collect Electronic Patient Reported Outcomes (ePRO) and Electronic Clinical Outcome Assessments (eCOA). We have approximately 20 ongoing or past studies that have successfully utilized Digital Health tools for data collection. Several illustrative examples follow.

In a recently completed atrial fibrillation study, we collected clinical, adverse event, and imaging data, 12-lead electrocardiogram (ECG) uploads, and participant-generated single-lead ECG using Digital Health tools. These data were securely transmitted daily from mobile phones and ECG devices into an encrypted database hosted in Microsoft Azure. Data were quality checked and combined for the final safety and efficacy analyses.

We collect eCOA and ePRO using tools such as MyCap. MyCap is a participant-facing mobile application for survey data collection and the automated administration of active tasks. Participants install the application onto their mobile device, enroll using a provided code, and complete surveys and, in some cases, upload requested photos and/or videos. These data are synchronized to the REDCap study database when the participant's mobile device is connected to the internet.

In the Prospective Evaluation, Analysis, and Kinetics of IV Sotalol (PEAKS) Registry, ECG recordings are performed with an FDA-approved mobile ECG device (Kardia 6L, AliveCor) in order to assess alternative QT monitoring approaches. The same device is also used to record post-discharge ECG tracings. The ECG device is synchronized with the participant's mobile device, where a vendor-specific mobile application is installed. Readings are then uploaded from the mobile device to a site portal. Each site portal transmits participant data to Utah DCC via an API, where the data are loaded into a central data warehouse.

The Utah DCC assisted the Four Corners Youth Concussion (4CYC) investigators in leveraging their clinical registry to support the submission and funding of a NINDS-funded CARE4Kids pediatric concussion study. In CARE4Kids, participants complete surveys on tablets in clinic and on their personal devices at home. The Utah DCC ensures the connectivity between participant submitted data, clinical data, the imaging repository, and three labs performing experiments on biospecimens.

In the AsA-NHPI Cohort Study, we will customize which Digital Health tools can be used. This is of course dependent on a) the data elements of interest identified during the UG3 phase of protocol development and b) what technology is available to participants. As an example, if a participant were not to have a smart phone, we can email questions, make a phone call, or collect data on paper.

E Data Management and Governance

E.1 Data Management

We describe the proposed data management process in this section, but complete details regarding the applications discussed are found in *Facilities and Other Resources*. For manual data entry, study information will be entered into the REDCap application by study site personnel. A nightly study export from the REDCap database to the CC SQL database will occur. This data warehouse is accessed by the Query Manager application which executes validation checks to identify discrepancies and generate the associated queries. CC data validation processes and reporting are operated through the data warehouse. The site coordinators log into the CC's instance of REDCap and Query Manager to resolve and respond to queries which completes the automated process of data cleaning.

Clinical events to be adjudicated will be reviewed by the Adjudication Committee. Within the REDCap database, a data entry form is created with access restricted to study adjudicators. Participant medical data are uploaded to REDCap to generate an adjudication dossier. The Utah DCC has experience conducting outcome adjudication via a variety of mechanisms, including "best-2-out-of-3" and group consensus meetings. Adjudicators review and enter data in REDCap (if adjudication is performed at an individual adjudicator level) or data are entered by the CC staff with Adjudication Committee guidance if adjudication is performed in a group consensus setting. Adjudicated data are included in nightly exports to the CC data warehouse for use by other study staff.

E.2 Data Governance

The Utah DCC approaches data governance via a modern, robust, and compliant mechanism. Common challenges in data governance include lack of senior leadership, uncertainty regarding "ownership" of the data, and

lack of visibility on data management practices to key stakeholders. In this proposal, we intend to utilize the Community Advisory Board (CAB) to advise the CC on data governance practices to address these challenges. The nature of the AsA-NHPI Cohort Study affords us the novel opportunity to engage members of the AsA and NHPI communities with special interest and expertise in the **culturally sensitive approaches to data governance**. We intend to utilize the outreach approaches of the Community Collaboration and Engagement Team (CCET) at the University of Utah Clinical and Translational Science Institute (CTSI) to identify members of the CAB. The CAB is more fully described in Section B.1.9 of *Overall Structure of the Study Team*. The process whereby CCET identifies participants for community engagement activities is described fully in Section E in *Facilities and Other Resources*.

F Management and Tracking of Capitated Funds to the CCFCs

The Utah DCC manages several networks in which capitated payments are managed, tracked, and disbursed by the DCC. We have found that paying a site based on “enrollment” alone can lead to a large proportion of missing data. Certain data elements and visits are more critical than others in answering study questions. We have experience working with recruiting sites to create visit requirements before a participant’s visit is eligible for payment. The conversation is typically jointly led by clinical and biostatistical leadership within the CC who can identify critical data elements and other requirements necessary for a visit to be eligible. These payment requirements are then discussed with the SC for official approval prior to implementation so expectations are clear before CCFC activation.

After payment requirements are identified, we will create reports that are accessible to the CCFCs that summarize their current participant visit payment eligibility. The report, an example of which is shown in Figure 3, details the capitated amounts for each research component (shown by clicking the blue arrow in the figure), in addition to summarizing current amounts due to the sites. This is one of several reports CCFCs will use to identify critical missing data. At pre-specified periods (e.g., quarterly), financial analysts at the Utah DCC will use the reports to issue capitated payments to the sites. This entire process has been streamlined over the past two decades and will be customized to fit the needs of the AsA-NHPI Cohort Study network.

| Site | StudySubjectID | Milestone | Subject Count | Amount Billable |
|------|----------------|---|---------------|-----------------|
| NWCH | NWCH-1002 | Clinical Sites (GRACE-2/TRIPS) - Initial phenotyping complete | 1 | \$300.00 |
| | | Total | 1 | \$300.00 |
| | | | 1 | \$300.00 |
| | | Grand Total | 1 | \$300.00 |

Figure 3: An example billing report from a current network utilizing capitated payments to sites

G Website and Participant Newsletter

G.1 Website

The Utah DCC has designed and developed numerous websites to support networks, studies, and projects. These websites are actively enhanced to maintain a modern aesthetic and to leverage modern functionality. The content for our websites will be developed by the CC in collaboration with the network PIs and the CAB to determine what content is most important. We have access to communications expertise to develop community facing materials. We anticipate the website will have features for both participants/communities (public-facing) as well as for Investigative teams (private). The public-facing website will have overall summaries of recruitment and the distributions of baseline characteristics of participants enrolled. We will provide an interactive experience

to evaluate outcome data based on select participant characteristics. An example of how we have previously implemented such a public-facing website is given in *Facilities and Other Resources*. The Investigative team (CC, CCFC, investigators, coordinators, and NIH) will have access to a private, secure section of the website. This will act as the first place investigators and coordinators will go to access information about the AsA-NHPI Cohort Study, including committee membership rosters, status reports, scientific news and updates, ancillary study proposals and their management, and manuscript proposals and their management. It is anticipated that the study's essential documents will be maintained securely in eRoom, as described in *Facilities and Other Resources* and *Budget Justification*.

G.2 Participant Newsletter

We believe the public, including participants enrolled, should be regularly updated on the study progress. In networks coordinated by the Utah DCC, we encourage regular newsletters as a way to report on research efforts to the participants and investigators. The newsletter includes updates on current research projects, lay summaries and links to latest publications, and related material such as short descriptions of collaborator's projects and participant spotlights. The content is developed by the Utah DCC in collaboration with the network PIs. The newsletter is designed to be distributed both electronically and in print. An example from a DCC network is shown in Figure 4. We intend to implement this process in the AsA-NHPI Cohort Study on a semi-annual basis during the study. We will translate the newsletter using University of Utah translational services provided via the Office of Research Participant Advocacy or TransPerfect into all languages that are being enrolled in the study. We have budgeted for this translation process accordingly.

The screenshot shows the homepage of the NPMSC Newsletter. The header features a large orange background with the text "NPMSC Newsletter" in white. Below the header, the title "The Network of Pediatric Multiple Sclerosis Centers (NPMSC)" is displayed in orange. A welcome message follows, encouraging readers to learn about research progress and network findings. To the left, a sidebar titled "What's Inside" lists several sections with corresponding page numbers: "Spotlights: Erick and the MS Youngsters" (page 2), "Study Updates" (page 3), "Research Findings" (page 4), "Who Are We?" (page 5), and "Latest Publications" (page 6). On the right side, there are three photographs: a girl named Julissa baking cookies, a boy named Erick standing outdoors, and a woman named Joe smiling. Below these photos, a caption reads "Don't miss the NPMSC spotlight featuring Erick and the MS Youngsters—page 2". Further down, a map of the United States highlights various states with stars, labeled "NPMSC Clinical Centers". At the bottom, the NPMSC logo is shown along with a call to action: "Interested in investing in this great cause? Visit the National MS Society's [website!](#)".

Figure 4: Example newsletter, as accessed on the network's website

Biosketches

Biosketches go here

Budget

Budget goes here

Budget Justification

The consolidated budget is shown in the table below and each component of the budget will be described separately in this narrative. We developed the budget justification based on the implied assumption from the RFA that 5% of participants will be enrolled in Year 2, the remaining 95% of participants will be equally enrolled across Years 3-5, and Years 6-7 will be meant for follow-up.

| Component | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 | Year 7 | Total |
|--------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|--------------|
| Personnel | \$1,185,069 | \$1,673,594 | \$1,748,449 | \$1,542,053 | \$1,254,529 | \$554,722 | \$520,579 | \$8,478,995 |
| Equipment | \$0 | \$0 | \$0 | \$0 | \$0 | \$0 | \$0 | \$0 |
| Travel | \$38,000 | \$30,000 | \$30,000 | \$30,000 | \$30,000 | \$22,000 | \$22,000 | \$202,000 |
| Other Direct Costs | \$465,027 | \$1,272,263 | \$4,634,749 | \$4,848,575 | \$5,140,764 | \$3,369,800 | \$2,949,289 | \$22,680,467 |

Key Personnel

We have budgeted key personnel assuming effort increases during the active enrollment years (compared to Year 1) and then reduces in effort in Years 6-7 during follow-up and maintenance mode. The increased effort in Years 2-5 will allow for active setup and participation on the various committees.

Jamie P. Dwyer, M.D., Multiple Principal Investigator/Contact, 2.4 CM (Year 1), 3.0 CM (Years 2-5), 1.8 CM (Years 6-7). Dr. Dwyer is Director of the Utah Data Coordinating Center (DCC), an adult nephrologist, and is experienced at implementing multi-center research. His clinical research has focused on the design, conduct, analysis, and reporting of large-scale multi-center studies across various therapeutic areas. Dr. Dwyer is the Director of the Clinical Research Support Office (CRSO) in the Clinical and Translational Science Institute (CTSI) at the University of Utah and the Associate Dean of Clinical Research at the University of Utah. His expertise centers around protocol design, medical monitoring, and study conduct. Dr. Dwyer will participate in all Asian American, Native Hawaiian and Pacific Islander (AsA-NHPI) Cohort Study activities and work collaboratively with the other Multiple Principal Investigators (MPI) Raphael and VanBuren and the Co-Investigators. Specifically, he will assume fiscal and administrative management including maintaining coordination with the CCFCs, oversight of the budget, maintenance of staffing of the CC, and supervision of the Co-Is. He will coordinate protocol development, thereby ensuring the study stays in scope and successfully transitions from the UG3 to the UH3 phase. Dr. Dwyer will assume responsibility for communication with the NIH and annual reporting requirements.

Kalani Raphael, M.D., Multiple Principal Investigator, 2.4 CM (Year 1), 3.0 CM (Years 2-5), 1.8 CM (Years 6-7). Dr. Raphael is an adult nephrologist who has strong ties to the Native Hawaiian and Pacific Islander (NHPI) communities. He is an established clinical and translational scientist with expertise in metabolic acidosis in chronic kidney disease. He will bring his clinical research expertise and cultural knowledge to help design and implement a protocol that is scientifically informative and culturally responsible. Dr. Raphael will be the primary CC contact for the Community Advisory Board, will oversee recruitment and retention efforts, and be the lead CC member for ancillary study proposals and implementation. Dr. Raphael will participate in all AsA-NHPI Cohort Study activities and work collaboratively with MPIs Dwyer and VanBuren and the Co-Investigators.

John M. VanBuren, Ph.D., Multiple Principal Investigator, 2.4 CM (Year 1), 3.0 CM (Years 2-5), 1.8 CM (Years 6-7). Dr. VanBuren is an expert in data and clinical coordinating center functions for multi-center research. He has been the lead biostatistician for several large research networks and multi-center studies coordinated by the Utah DCC. Dr. VanBuren will be responsible for overseeing the CC's day-to-day efforts and activities, including ensuring that appropriate data are collected to accomplish the goals of the study. Dr. VanBuren will participate in study investigator teleconferences and project meetings, oversee development of analysis datasets, as well as provide statistical expertise for the project. Dr. VanBuren will oversee the presentation of results to the Observational and Safety Monitoring Board (OSMB), oversee final analyses, and assist in abstract and manuscript preparation.

Katherine A. Sward, Ph.D., R.N., M.S., Co-Investigator, 1.2 CM (Year 1), 2.4 CM (Years 2-5), 0.6 CM (Years 6-7). Dr. Sward is responsible for overseeing data harmonization efforts for the AsA-NHPI Cohort Study, super-

vising other informatics faculty, as well as providing the administrative infrastructure for 21 CFR §11 compliance. She will be responsible for identifying the daily activities related to identifying and mapping common data elements. She oversees informatics efforts on interoperability—including common data elements, forms, and a standardized approach to constructing study databases. Dr. Sward will also be responsible to oversee the extraction of the final AsA-NHPI Cohort Study database that will be made available as part of the Resource Sharing Plan. She will meet at least biweekly with the CC and conduct meetings with informatics faculty collaborating to support the AsA-NHPI Cohort Study. Dr. Sward will participate in the Environmental & Lung Disease Working Group.

Brian R. W. Baucom, Ph.D., Co-Investigator, 1.2 CM (Year 1), 1.8 CM (Years 2-5), 0.6 CM (Years 6-7). Dr. Baucom is responsible for bringing mental health data coordination and common data element expertise to the AsA-NHPI Cohort Study. He has more than 20 years of experience collecting and analyzing data relating to psychological distress, psychopathology, and chronic health conditions. He will help in the creation of the protocol, data element development, and analysis of mental health outcomes. He will work closely with Dr. Sward during the creation of the database. Dr. Baucom will participate in the Mental Health Working Group.

Kevin Shah, M.D., Co-Investigator, 1.2 CM (Year 1), 1.8 CM (Years 2-5), 0.6 CM (Years 6-7). Dr. Shah will provide clinical expertise relating the analysis and interpretation of cardiovascular outcomes. He will work closely with the other Co-Investigators during the creation of the database to help ensure appropriate capture of clinical data. With his experience in the South Asian communities, he will work closely with Dr. Raphael to ensure cultural appropriateness in documents produced by the CC. Dr. Shah will participate on the Adjudication Committee and will provide clinical expertise to the CC staff during analyses of data collected from the study.

Yue Zhang, Ph.D., Co-Investigator, 0.6 CM (Years 1), 1.2 CM (Years 2-5), 0.6 CM (Years 6-7). Dr. Zhang will work closely with Dr. VanBuren to help ensure statistically appropriate analyses are performed by the CC in the AsA-NHPI Cohort Study. Dr. Zhang will bring his expertise particularly in multi-state modeling and environmental statistics to the CC. He will guide the CC staff statisticians in the linkage of publicly available external health datasets (e.g., air quality sensors) and all analyses relating to environmental exposure and multi-state modeling. In addition, Dr. Zhang will serve on the Environmental & Lung Disease Working Group.

Christy Porucznik, Ph.D., Co-Investigator, 0.6 CM (Years 1), 1.2 CM (Years 2-5), 0.6 CM (Years 6-7). Dr. Porucznik will provide extensive cohort study experience to the CC in the AsA-NHPI Cohort Study. She will bring expertise in home-based data collection. During enrollment, she will bring best practices from past experience to help ensure this cohort study has successful recruitment and retention. Dr. Porucznik will serve on the Recruitment and Retention Committee, the Quality Committee, and the Biospecimen Committee.

Other Personnel

Unless otherwise specified below, we have structured the other personnel effort in a similar manner to key personnel where effort is higher during enrollment years.

Stephanie Dorton, BS, Director, 6.0 CM (Years 1-5), 2.4 CM (Years 6-7) The Director of the AsA-NHPI Cohort Study will work with Dr. Dwyer to oversee the financial management of the CC budget and the overall management of the project. The Director will act as a liaison to the CC and serve as a central point of communication for the CC activities. She will assure that the CC team is functioning efficiently to support the project. The Director will help oversee the development of the manual of operations, assure new regulatory requirements are addressed throughout the study, and replace and train team members if there is a staff change at the CC. She will assure the risk assessment document is up to date and that risks are documented in accordance with regulations. The Director will also oversee the Project Manager and ensure the project milestones are being met. She will meet weekly with Drs. Dwyer, Raphael, and VanBuren during the MPI meeting.

Michelle Robinson, BS, Project Manager, 12.0 CM (Years 1-5), 3.6 CM (Years 6-7) The Project Manager will be responsible for interfacing with the CCFCs, helping to develop the protocol and will work with the Clinical Data Manager to develop data variables and the data flow. She will interface with the CCFCs to assure the clinical sites can collect the data as specified. The Project Manager will develop the Manual of Operations and any training materials including online training as appropriate. The Project Manager establishes and completes a risk assessment document and creates a plan to mitigate risks identified. The Project Manager will also be responsible for conducting remote monitoring activities as needed to verify data quality and protocol compliance. She will work with the on-site monitor and ensure the monitor has the activities needed for monitoring. The Project Manager will manage the CCFCs research coordinators' access to the database and CC systems and will conduct teleconference calls as needed. She will help the data manager with final data cleaning, data lock, and site closeout. The Project Manager regularly meets with the Project Manager Professional (PMP) to ensure timelines are being met and identifies concerning areas to the critical path that potentially jeopardizes study integrity. She will interact with the single IRB (at Utah) on behalf of all of the sites. With the guidance of several committees, the Project Manager will draft the newsletter, draft the data book, and ensure website content is accurate. She will also ensure clinicaltrials.gov is updated if registered.

Frances Sebahar, BS, Project Manager, 3.0 CM (Year 1), 6.0 CM (Years 2-3) The second Project Manager will be responsible for supporting the lead project manager (Ms. Robinson) in the setup of the study and changes that occur in the first year of the study.

Megan Varner, BS, Clinical Data Manager, 9.0 CM (Year 1), 12.0 CM (Years 2-4), 10.8 CM (Year 5), 4.8 CM (Years 6-7) The Clinical Data Manager will be responsible for identifying the data variables from the study protocol. She will also develop the database plan and create the electronic data capture system that sites will use to enter the data. She will be responsible for day-to-day monitoring of data submitted from the individual sites. She will prepare regular internal and external reports concerning data quality, and work closely with the Project Manager to determine areas of needed additional training at each site. The Clinical Data Manager will work closely with Ms. Fuller to 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 Clinical Data Manager will monitor query resolution status. She will work closely with IT to help sites customize each site's automatic data pull. The Clinical Data Manager will also lock data prior to OSMB reviews, and will make any database changes, or update the database variables as necessary. She will lock the final dataset prior to study analyses.

Bethany Fuller, BS, Clinical Data Manager, 6.0 CM (Years 2-3) The second Clinical Data Manager will work with Ms. Varner on this project. Ms. Fuller will primarily be responsible for writing and resolving discrepancy checks (queries) for these two years while sites are onboarded and learning the database.

Russell Banks, MS, Statistician, 9.0 CM (Year 1), 12.0 CM (Years 2-5), 6.0 CM (Years 6-7) The Statistician will be primarily responsible for data analysis. He will work with Drs. VanBuren and Zhang to conduct all statistical analyses and preparation of reports. The Statistician will prepare formal interim data reports and provide all OSMB reports based on locked data at intervals during the trial. The Statistician will work with Mr. Boone to review all manuscript requests and create manuscript analysis plans for individual manuscripts as requested by the Principal Investigators. The manuscript plans will be coded and implemented during and after the enrollment period. Data will be checked for missingness and accuracy. Final data analyses and dataset preparation will be done in year 7 at the close out of the study. The Statistician will assist with all manuscript preparation and public-use dataset creation. The Statistician will also produce all tables, listings, and figures needed for the Data Book.

Bobby Boone, MS, Statistician, 6.0 CM (Years 3-5) The second Statistician will work closely with Mr. Banks (lead staff Statistician) during the main enrolling years to plan and code potential manuscripts.

Brent Hulsey, BS, PMP, Project Manager Professional, 9.0 CM (Years 1-3), 6.0 CM (Years 4-5), 1.2 CM (Years 6-7) The Project Manager Professional (PMP) will ensure communication, timelines, and deliverables within the

CC team. They will communicate with the CC Project Manager any changes or issues that need to be discussed with the scientific team. The PMP will attend regular team meetings to discuss study needs, study progress and development, and may attend key strategic meetings and calls. The PMP will produce Gantt charts to help the Steering Committee understand timeline during both study startup and enrollment.

Ben Fisher, MS. Regulatory Coordinator, 1.2 CM (Year 1), 3.0 CM (Years 2-3) The Regulatory Coordinator will assist and oversee the project manager with completion of the risk assessment and risk management plan for the AsA-NHPI Cohort Study. He has assisted in the preparation of many risk management plans. He has regulatory experience and continuously updates the Utah DCC risk plans to reflect federal and international regulations. He will assure that risks are appropriately identified and mitigated at the beginning of the study. He will also help assure that the reports that are produced by the CC study team reflect key risks and the study outcomes. He will oversee the on-site monitor to ensure the risk-based monitoring plan is implemented appropriately. He will provide consultation on any regulations that affect the study.

John Brumett, Software Design Engineer/Data Transfer Specialist, 6.0 CM (Year 1), 9.0 CM (Years 2-4), 3.0 CM (Years 5-6), 1.2 CM (Year 7) Mr. Brumett will design, develop, and maintain the website. Mr. Brumett has over 10 years of experience as a full-stack developer. He has expertise in user experience (UX) design, data modeling and database design. He will design and develop the AsA-NHPI Cohort Study website, leveraging tools and languages including cascading style sheets (CSS), PHP, UX, JavaScript (JS), WordPress and MySQL. Mr. Brumett will partner with the Sr. IT Project Manager to onboard submitting sites to their preferred method of data transfer (e.g., automated transfer from EHR, EDC to EDC API, etc.).

Christine Mahler, Business Intelligence (BI) Developer, 9.0 CM (Year 1), 12.0 CM (Years 2-4), 6.0 CM (Year 5), 1.2 CM (Years 6-7) Ms. Mahler will design, develop, and maintain the Tableau dashboards and other reports. Ms. Mahler has 10 years of experience in database development, database architecture, and dashboard development. She will design the front-end Tableau dashboards as well as architect the back-end infrastructure to support the secure movement of data throughout the data ecosystem. She will use her training in UX design and performance optimization to ensure dashboards and reports are responsive and intuitive.

Sujata Shinde, BI Developer, 6.0 CM (Years 2-3) Ms. Shinde will work closely with Ms. Mahler in Years 2 and 3 to develop, code, and implement BI reports. We expect after Year 3 all major modifications to reports will have been implemented based on the observed enrolling data.

Tara Merrill, J.D., Contracts Manager, 3.0 CM (Years 1-4), 1.2 CM (Years 5-6) Ms. Merrill will be responsible for establishing the contractual relationships between the CC and each enrolling site's organization. She has experience with establishing Data Use Agreements, Business Associate Agreements, and other contracts for the Utah DCC.

MaryAnn Howard, Financial Analyst, 3.0 CM (Year 1), 6.0 CM (Years 2-4), 3.0 CM (Year 5), 1.2 CM (Years 6-7) Ms. Howard will be responsible for issuing capitated payments for site enrollment and ongoing oversight of the budget with Dr. Dwyer. She will provide input to the setup of the financial reports and work with sites to answer any questions regarding payment processes.

Michelle Wilcox, BS, Administrative Assistant, 12.0 CM (Years 1-7) Ms. Wilcox will be responsible for setting up and organizing internal CC meetings, setting up study-specific webinars that may be recorded, organizing study documents at the CC in our electronic storage system, and assuring that regulatory documents are stored and easily accessible. The Administrative Assistant will also take minutes of meetings and will assist with setting up key study meetings with investigators, sites or others as requested (e.g., travel arrangements, conference logistical planning). The Administrative Assistant will also be responsible for assisting with organizing training materials on our electronic learning platform as needed. Ms. Wilcox is the social media administrator for the Utah DCC, and she will take on all social media tasks for the AsA-NHPI Cohort Study.

Equipment

No funds are requested for equipment.

Travel (\$202,000 across all 7 years)

Travel expenses are requested for Steering Committee meetings each year of the proposal. We anticipate 3 in-person meetings in Year 1 to help establish the network, 2 in-person meetings Years 2-5 during enrollment, and 1 in-person meeting in Years 6-7 while follow-up is ongoing. We estimate \$2,000 per person per meeting (covers air travel, hotel, and per-diem costs). Per guidance in the RFA, we budget for 3 person-trips each meeting. (\$2,000 per traveler x 3 travelers per study x 3 meetings = \$18,000 in Year 1; \$2,000 per traveler x 3 travelers per study x 2 meetings = \$12,000 per year in Years 2-5; \$2,000 per traveler x 3 travelers per study x 1 meeting = \$6,000 per year in Years 6-7). We also budget for a Study Chair to attend Steering Committee meetings. Using \$2,000 per meeting and the same meeting structure described, this leads to \$6,000 in Year 1, \$4,000 in each Year 2-5, and \$2,000 in each Year 6-7. We budget for OSMB members travel each year of the proposal. Costs are estimated for 1 trip, with 7 person-trips each meeting. (\$2,000 per traveler x 7 travelers per meeting = \$14,000 per year).

Other Direct Costs (\$22,680,467 across all 7 years)

Materials and Supplies (\$60,000 across all 7 years)

We budget \$5,000 for the replacement of 2 laptops per year. In Years 3-7 we budget an additional \$5,000 a year for printing materials and shipping materials to sites (when needed).

Publication Fees (\$50,000 across all 7 years)

We budget \$2,500 per year in Years 1 and 2, \$5,000 in Year 3, \$7,500 in Year 4, \$10,000 per year in Years 5 and 6, and \$12,500 in Year 7 for publication fees. Initial years will publish on operational items (e.g., protocol) while later years will publish on enrollment and follow-up data.

Honoraria (\$119,947 across all 7 years)

- **OSMB** We are requesting an honorarium of \$500 per OSMB member (n=7) for each meeting per year (1 in person and 1 virtual). This results in \$7,000 per year for a total of \$49,000 across Years 1-7.
- **Study Chair** We are requesting an honorarium of \$500 a day for each in-person meeting the Study Chair attends. Planning for 3 in-person 2-day meetings in Year 1 (\$3,000), 2 in-person meetings in Years 2-5 (\$2,000 each year), and 1 in-person meeting in Years 6-7 (\$1,000 each year), this results in a total of \$13,000 across Years 1-7.
- **Community Advisory Board** The Community Advisory Board is budgeted at \$9,631 in Year 1 for the setup and initial meetings. This includes national identification of CAB members. Years 2-7 CAB fees are \$7,470, \$7,694, \$7,924, \$8,162, \$8,407, \$8,659, respectively. These costs correspond to the CCET setup and maintenance which includes creation of meeting minutes. Additionally, members are provided compensation for participation in each meeting. CCET will identify additional members if a member withdraws. This results in \$57,947 across all 7 years

Translations (\$108,000 across all 7 years)

- **Newsletter** We anticipate releasing 2 public-facing newsletters per year and are anticipating translating them into 10 languages. The average quote for translation across the 10 most common AsA and NHPI languages for a 6-page public-facing newsletter like we usually publish is \$800 per translation. This would result in \$16,000 per year in Years 3-7 (we will start newsletter in Year 3 once 500 participants are enrolled in Year 2). This results in a total of \$80,000 across Years 1-7.
- **Consent Forms** We plan on translating the consent forms into all common languages at the enrolling sites. For budgetary purposes, we are planning on 10 translations at \$800 per translation in Year 1 (\$8,000 in

Year 1). Updates to the consent form are anticipated each year and we budget \$1,000 a year for Years 2-7. This results in a total of \$14,000 in Years 1-7.

- **Participant-facing Documents** Participant-facing documents (e.g., surveys sent to the participant) will need translation. For budgetary purposes, we are planning on 10 translations of participating documents at \$800 per translation in Year 1 (\$8,000 in Year 1). Updates to the participating documents and additional surveys are anticipated each year and we budget \$1,000 a year for Years 2-7. This results in a total of \$14,000 in Years 1-7.

Automatic Data Transfer (\$150,000 across all 7 years)

We are budgeting \$25,000 per site in Year 2 to go to the sites to support the setup of automatic data transfer.

Florence eBinder (\$7,000 across all 7 years)

Yearly renewal fee for the online regulatory document storage platform for participating sites. (\$1,000/year x 7 years)

eRoom (\$33,866 across all 7 years)

We budget for 6 eRoom licenses per site and 5 additional eRoom licenses for use by NIH staff. At \$118 per license per year, this results in \$4,838 per year for Years 1-7.

Onsite Monitoring (\$382,500 across all 7 years)

Remote monitoring costs are reflected through the Project Management effort. On-site monitoring is planned for supplementing remote monitoring. We have budgeted for 1 onsite monitoring visit in Year 2, 4 onsite monitoring visits per year in Years 2-5, and 2 onsite monitoring visits per year in Years 6-7 at \$3,750 per visit. This results in $\$3,750 \times 6 \text{ sites} = \$22,500$ in Year 2, \$90,000 each year in Years 3-5, and \$45,000 each year in Years 6-7. The site monitor will travel to the site to meet with the PI and site research staff, review records and evaluate data quality. Costs are for contracted monitor hourly rates and travel costs anticipating sites will include non-continental US sites (e.g., Hawai'i).

DCC IT Recharge Center Fee-for-Service (\$653,467 across all 7 years)

An essential component of the proposed Coordinating Center is a large Information Technology infrastructure, necessary to support all research projects utilizing the Utah DCC staff 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 Full-Time Equivalents (FTE) on a research project that utilizes the DCC, and subsequently DCC IT, 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 cost of \$653,467 over the project period for this service.

REDCap (\$35,000 across all 7 years)

Maintenance of the EDC to maintain 21 CFR §11 Compliance is budgeted at \$5,000 per year.

Website (\$60,000 across all 7 years)

We budget \$30,000 for the initial setup and creation of the website in Year 1 and \$5,000 per year in Years 2-7 for maintenance.

Tableau (\$175,000 across all 7 years)

We budget \$25,000 per year to support the Tableau costs that are used for internal (to the network) and public-facing reports.

SIRB (\$243,600 across all 7 years)

We are assuming there will be 6 CCFCs and each CCFC will have up to 5 enrolling sites that require oversight by the SIRB (i.e., 30 total “sites” monitored by the SIRB). Initial protocol review and site evaluation is budgeted at \$69,600 in Year 1. Annual protocol review is free and annual review is \$29,000 per year.

Steering Committee Meetings (\$260,000 across all 7 years)

Steering Committee meetings are budgeted for \$20,000 per 2-day meeting. We plan 3 meetings in Year 1, 2 meetings per year in Years 2-5, and 1 meeting per year in Years 6-7. This results in \$60,000 in Year 1, \$40,000 per year in Years 2-5, and \$20,000 per year in Years 6-7.

Conferences (\$35,000 across all 7 years)

Expenses are requested for CC to attend conferences to present novel Coordinating Center findings. Costs are estimated at \$2,500 per person, which covers transportation, stay, and registration at the conference. We budget 1 conference per year for 2 CC faculty and/or staff.

Capitated Payments (\$15,920,000 across all 7 years)

Per the RFA, we are budgeting \$350K, \$2.2M, \$2.2M, \$2.2M, \$1.5M, and \$1.5M in years 2-7 for direct capitated payments. We are assuming there will be a 60% average indirect rate for these capitated payments that will be issued to the site. This results in \$560K, \$3.520M, \$3.520M, \$3.520M, \$2.4M, and \$2.4M in years 2-7 for total capitated payments (direct & indirect). The University of Utah has waived indirects on all site capitated payments. See letter of support from Dr. Erin Rothwell.

Biorepository (\$1,103,697 across all 7 years)

The University of Utah Cellular Translational Research Core (CTRC) will serve as the biorepository for the cohort study. The biorepository will receive, process, aliquot, and store biospecimens at -80 degrees C. The biorepository will also be responsible for identifying and selecting samples to be shipped to investigators when needed. Costs of the average participant for enrollment in Years 2-5 is \$161 per participant. For DNA and RNA, this includes frozen storage of blood in the appropriate PAXgene tube, but not extraction. For serum, plasma, and urine this includes isolation and aliquot. We budget for 2 hours of consultation with the biorepository manager a year at \$88 an hour to discuss maintenance and quarterly check-in. We have factored into the budget that total storage costs will increase each month as new boxes are added to previously stored cryoboxes in the biorepository. This corresponds to a total biorepository budget of \$156; \$23,381; \$153,401; \$188,961; \$336,651; \$194,166; and \$206,981 for Years 1-7, respectively.

Central Laboratory (\$3,283,391 across all 7 years)

Associated Regional and University Pathologists, Inc. (ARUP) will serve as the central laboratory for the cohort study. Costs in year 1 include the initial project setup fee (\$30,000) and 50% of the project management fee (\$74,840); the remaining 50% of the project management fee (\$74,840) is due at study close out (year 7). \$187,100 is charged as a specimen return where leftover samples from the central lab are transported to the

biorepository for storage. We understand that tests to be performed as part of the protocol have yet to be determined. Below, we provide an example of a list of tests that could be performed in the 10,000 participants at baseline and at one follow-up visit. We assume a kitting cost of \$50 per visit and \$187.10 in laboratory costs. With the assumption that 500, 3167, 3167 and 3166 participants are enrolled in Years 2-5 respectively and follow-up laboratory draws occur 2 years later, this results in \$128,825; \$244,097; \$568,120; \$762,167; \$927,768; \$543,070, and \$109,344 in Years 1-7 respectively.

- CBC with platelet count and automated differential
- comprehensive metabolic panel
- high sensitivity c-reactive protein
- hemoglobin A1c
- total homocysteine
- lipid panel with direct LDL
- lipoprotein(a)
- troponin T, high sensitivity
- uric acid
- urine albumin-creatinine ratio.

Indirect Costs

Indirect costs are calculated based on the Modified Total Direct Costs at the University of Utah's federally negotiated rate for "Research." The University of Utah indirect cost rate for each year is calculated at 54%.

Study Timeline

The ASA-NHPI Cohort Study timeline is categorized by Startup, Enrollment, and Follow-up, and is shown in Figure 1. Additional details regarding analyses, publications, and OSMB meetings are also shown.

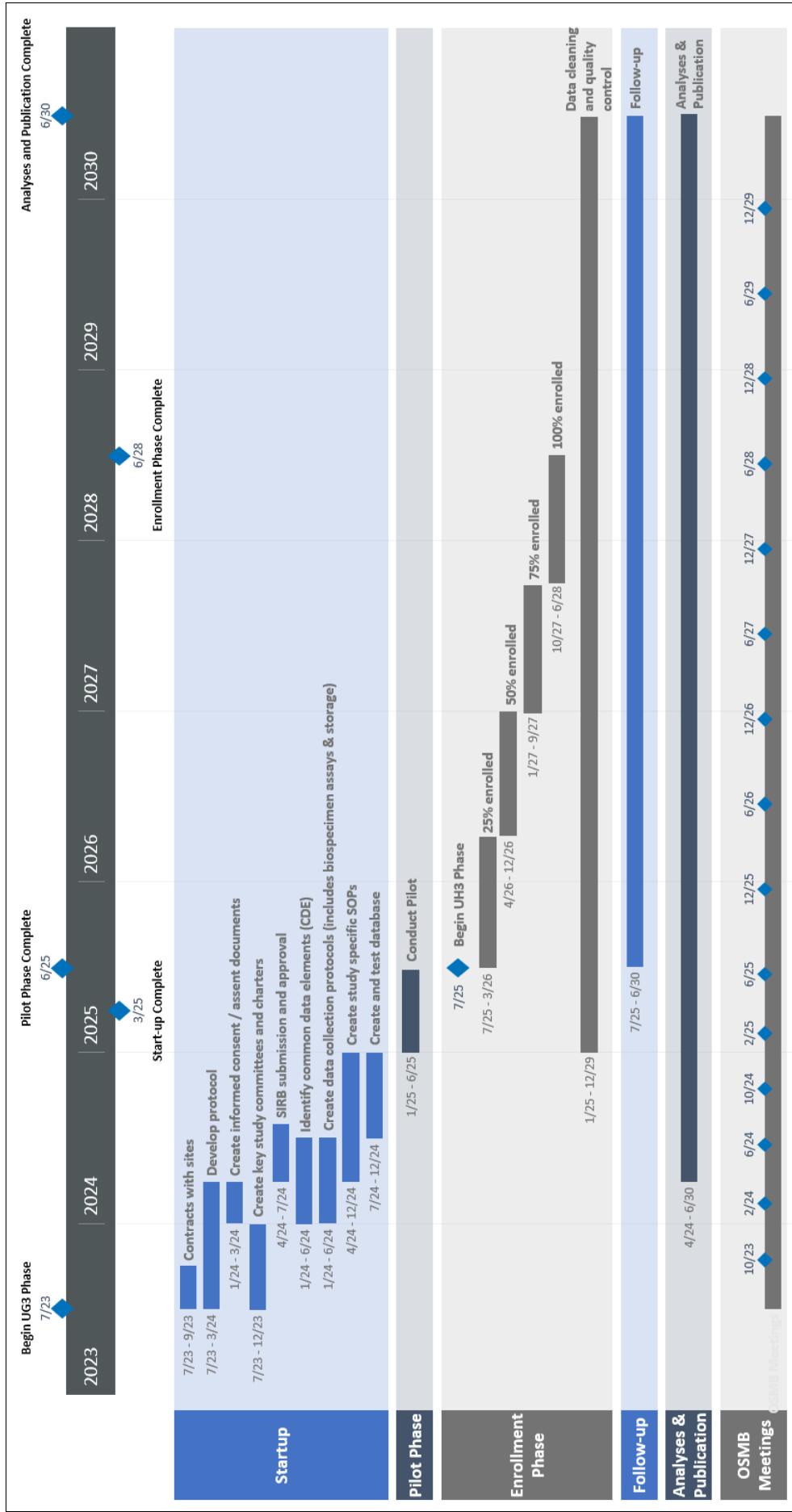


Figure 1: High-level timeline of the AsA-NHPI Cohort Study

Overall Structure of the Study Team

We propose a typical network organizational structure for the AsA-NHPI Cohort Study, as depicted in Figure 1.

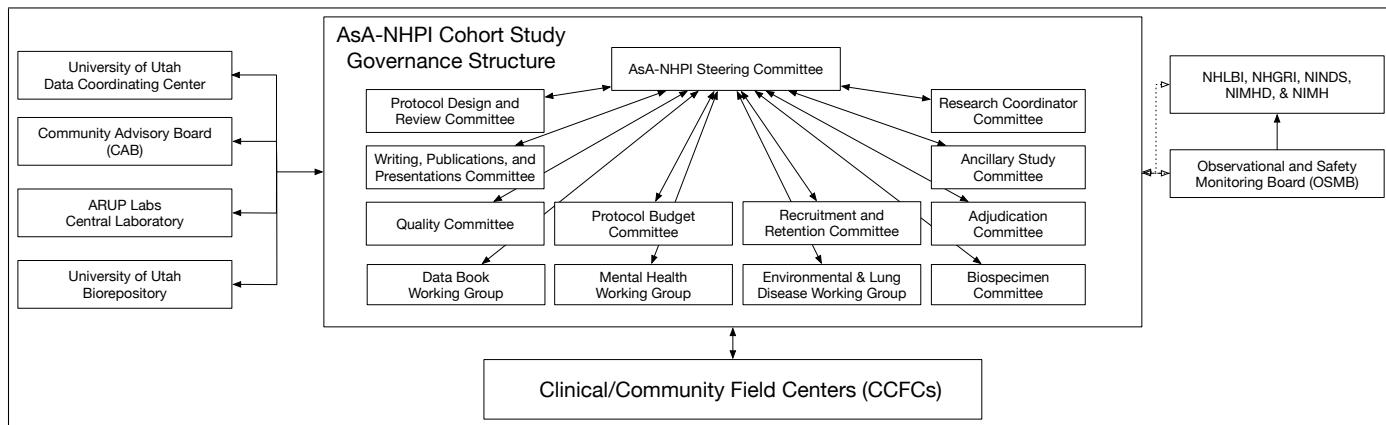


Figure 1: AsA-NHPI Cohort Study Organizational Chart

A AsA-NHPI Cohort Study Sites and Central Resources

A.1 Coordinating Center: Utah Data Coordinating Center

The Utah Data Coordinating Center (DCC) is thoroughly described in the *Facilities and Other Resources*. Utah investigators are described in their biosketches and their relationships in the *MPI Plan*.

A.1.1 CC Study Staff

The project managers (PM) provide leadership and coordination for daily study activities. They are an integral part of the Manual of Operations Committee (Section B.1.10) to assist in the production and maintenance of the Manual, as well as training materials. The data managers design and build the database used to centrally collect site data. They write discrepancy rules and help validate study results. The statisticians provide statistical review of databases, and design and implement all manuscript analyses and OSMB materials. The IT PM helps maintain timelines and produces tables and figures allowing the study team to understand critical paths in startup and enrollment. The IT and Business Intelligence (BI) personnel maintain the website, establish the requirements for automatic data transfers, and design and code reports. The regulatory coordinator helps draft and implement the risk-based approaches for monitoring. The administrative assistant helps with daily operations and records minutes from meetings. A thorough description of personnel and their activities can be found in *Budget Justification*.

A.1.2 Staff Supervision and Working Relationships with CCFCs

The MPIs will share responsibilities for allocating personnel resources. The cadence of meeting frequency for CC staff will be determined by the study needs but is anticipated to be at least weekly to facilitate the working relationships with the CCFCs. Dr. VanBuren will attend all staff meetings to ensure uniformity and productivity of day-to-day CC operations.

PMs are the point of first contact for the CCFC investigators and staff. If issues are identified by the CC or CCFC, the PM will bring it to the staff, summarize the issue, and develop a proposal to address it. If the issue requires escalation, Dr. VanBuren will raise the issue with the MPI team and/or Co-Is. The MPIs may re-allocate resources if necessary to address the issue.

A.2 Enrolling Sites: Clinical/Community Field Centers

We anticipate study participants will be recruited from 4-6 CCFCs located across the United States. We expect the cities and population enrolled will be diverse. We assume each CCFC will have the necessary personnel (e.g., PIs, Co-Is, coordinators) and research infrastructure (e.g., community outreach access, physical locations for participant recruitment) necessary to conduct this cohort study. Visits may be conducted in the clinics, the field, the home, remotely, or other location suitable to the participant and the CCFCs.

A.3 Central Laboratory: ARUP

Associated Regional and University Pathologists, Inc Laboratories (ARUP Labs, colloquially called ARUP), located in Salt Lake City, UT, will function as the central laboratory. ARUP is a nonprofit entity of the University of Utah, founded in 1984. Over the past nearly 40 years, ARUP has grown substantially to perform over 3,000 unique tests and test combinations, serving as one of the nation's largest reference laboratories. Ninety-eight percent (98%) of testing is performed in-house. Complete details regarding the testing requested and adherence to Good Laboratory Practice (GLP) and other federal regulations are described in *Biospecimen Plan*.

A.4 Biorepository: University of Utah

The Cellular Translational Research Core (CTRC) of the Clinical and Translational Science Institute (CTSI) at the University of Utah will function as the dedicated biorepository. The CTRC has been processing and storing human biospecimens for over 30 years at the University of Utah. CTRC provides stem cell, molecular biology, and biobanking services to support early translational and precision medicine research conducted by clinical researchers and basic scientists across the country. Complete details regarding the samples requested to be stored and adherence to GLP and other federal regulations are described in *Biospecimen Plan*.

B Committee Structure

B.1 Steering Committee

A charter that fully describes decision-making processes, conflict resolution, and quorum will be developed in the UG3 phase. This committee will be chaired by an independent SC Chairperson, who will be selected in collaboration with the CCFCs and appointed with approval of the NHLBI program officer. This Chairperson will not be affiliated with any of the institutions represented. The SC will meet by webinar monthly. SC meetings will initially be focused on initiation of the multi-center cohort study and meeting the milestones delineated in the *Study Timeline*. After implementation of the cohort study, in addition to discussing study implementation, a standing agenda item of the SC will be discussion regarding the development of new research concepts that can be developed into NIH-funded, peer-reviewed ancillary studies that can leverage the unique AsA-NHPI Cohort Study infrastructure and individual site strengths. The SC will meet (aside from the monthly webinars) for a full SC meeting up to three times per year in person. The CC will coordinate all meeting logistics. Specific committees and working groups will report in an advisory manner to the SC on a regular basis. We anticipate clinical areas of interest will include mental health, environmental, and lung disease, and as such have proposed working groups for these conditions. We anticipate most cardiovascular disease interest will organize around the Adjudication Committee.

B.1.1 Protocol Design and Review, and Protocol Budget Committees

The initial charge of the Protocol Design and Review Committee will be to direct the design of the AsA-NHPI Cohort Study. Similarly, the Protocol Budget Committee will function to determine the budgetary needs of the protocol developed in the UG3 phase. After the protocol is finalized in the UG3 phase, these committees will not be dissolved, but rather work towards the development of ancillary studies. After review by the Ancillary Study Committee and approval to move forward by the SC, new projects (i.e., ancillary studies) proposed by AsA-NHPI Cohort Study or other external investigators move into project development. The process of project development is detailed in Section C. The Protocol Design and Review Committee will work with the investigator to provide

in-depth scientific feedback and assistance with developing the concept into a mini-protocol. This committee may also be consulted by the investigator at later stages of development into a full protocol synopsis that can be attached to an NIH grant application. In parallel, the Protocol Budget Committee works with the investigator to define a realistic budget for the proposal. The Protocol Design and Review Committee will include at least 3 interested AsA-NHPI Cohort Study investigators and a CC biostatistician. The Protocol Budget Committee will include at least 3 interested AsA-NHPI Cohort Study investigators and must also include at least 3 AsA-NHPI Cohort Study research coordinators and CC staff. These committees will report to the SC when the mini-protocol is presented to the SC for its approval to move forward.

B.1.2 Recruitment and Retention Committee

The Recruitment and Retention Committee will include at least 3 interested AsA-NHPI Cohort Study investigators and must also include at least 3 AsA-NHPI Cohort Study research coordinators and CC staff. They will develop recruitment materials (e.g., advertisements for the community, participant pamphlets), assist in writing study consent form language, and monitor recruitment and retention across sites. This committee will be responsible for working with sites that are under-enrolling or have poor follow-up and will help them determine ways to improve recruitment and retention. Drs. Raphael and Porucznik will both serve on this committee.

B.1.3 Research Coordinator Committee

The Research Coordinator Committee will include the primary research coordinator from every CCFC site, and the lead PM from the CC. This committee will meet at least monthly and is responsible to provide advice to the SC about workflows to facilitate study startup, on-going participant accrual, and new problems or risks to the study success. The committee will also identify obstacles to study implementation or participant accrual encountered by the cohort study research coordinators. They will work closely with the Recruitment and Retention Committee and might have members that overlap.

B.1.4 Quality Committee

The Quality Committee will review the proposed study in this application, all project concepts that have progressed to the protocol level, and assess study-specific risks. Prospective preparation of a risk assessment and a risk mitigation plan is now a standard part of Good Clinical Practice (GCP) and will govern risk-based monitoring that will be conducted by the CC for the study. The Utah DCC has a regulatory affairs, compliance, and quality team that is accessible by all studies, and can provide tools to the Quality Committee to guide its activities. Co-I Dr. Porucznik will serve on this committee.

B.1.5 Writing, Publications, and Presentations Committee

The Writing, Publications, and Presentations Committee will review potential manuscript ideas and determine which of those ideas are suitable for analysis by the CC. After an idea is approved by this committee and SC, the Writing, Publications, and Presentations Committee will define the roles of each author, including the order of authorship, for publications arising from the AsA-NHPI Cohort Study. This committee will report regularly to the SC to present progress with respect to manuscript preparation. It is expected that manuscripts will be submitted for peer-reviewed publication within six months of data lock of any AsA-NHPI analyses provided. If there are abstract presentations prior to completion of the study, a manuscript is expected to be submitted within six months of the abstract presentation. If these milestones are not met, the SC may direct this committee to reassign the first authorship to an alternate investigator. The committee will consist of AsA-NHPI Cohort Study investigators, including CC biostatisticians, and will review manuscripts prior to submission to journals for publication. The purpose of this review is to improve the quality of network submissions and increase the speed with which results are disseminated via publication. Reviewer suggestions may be mandatory or optional; if there are mandatory revisions requested by the Writing, Publications, and Presentations Committee, then the manuscript must be brought back to the committee chairperson to verify that required changes have been made. This committee may implement a similar process of review for abstracts and presentations.

B.1.6 Adjudication Committee

We anticipate there will be several clinical outcomes of interest where collected data will require adjudication. After the set of common data elements are determined, we will establish the appropriate clinical domain experts needed for the Adjudication Committee. We will establish a charter that defines quorum, identifies the events requiring adjudication, defines those events, and outlines the members required to adjudicate each type of event. Rules, which may be established during the conduct of outcome adjudication, will be collated, adhered to, and potentially used to revise the charter as needed. The meeting frequency for the Adjudication Committee will vary depending on the number of events to be reviewed. Adjudication Committee members may be clinicians outside of the network depending on the need of the adjudication. We anticipate the flow of the Adjudication Committee meetings to start with the events that require the largest number and types of experts (e.g., death), and then allow members to leave the meeting as we progress to outcomes requiring a much narrower expertise (e.g., stroke). Drs. Dwyer and Raphael (two of the MPIs) have experience as members of and chairing adjudication committees and they will be responsible for developing the charter and leading the meetings. Co-I Dr. Shah, a cardiologist, will participate on the Adjudication Committee.

B.1.7 Ancillary Study Committee

We anticipate the AsA-NHPI Cohort Study will generate immense enthusiasm for investigation and analysis of this underrepresented population, and as such we foresee a need for an Ancillary Study Committee. The Ancillary Study Committee will advise the SC on key areas for investigation in the AsA-NHPI Cohort Study network, and the SC will authorize this committee to solicit and evaluate proposals. This committee will review all potential new projects, and once approved by the Ancillary Study Committee, the project will begin the ancillary study development process (further described in Section C). We anticipate a wide range of study types to be proposed that utilize the collected data and stored samples for the Ancillary Study Committee to review and recommend for further support in the network. This committee will be composed of appropriate clinical domain experts who reflect the areas of investigation evaluated by this cohort study.

B.1.8 Biospecimen Committee

The Biospecimen Committee acts as an advisory body to the SC, composed of at least 3 CCFC investigators. Ad hoc members may include study-assigned PMs or leadership from the central lab and biorepository. The committee will develop standard procedures for handling specimens and specimen-related study data requests, including both central lab and biorepository. They will develop the application requirements, including rationale, preliminary data, specific requests, plans for data sharing, timeline, and publication planning. They review applications and requests for biorepository samples, but do not make the final decision on the approval of specimen usage. The committee presents the proposal and its recommendation to the SC for a vote. Drs. Raphael and Porucznik will both serve on this committee.

B.1.9 Community Advisory Board

The Community Advisory Board (CAB) for the CC is distinct from the CABs for the CCFCs. The purpose of the CC's CAB is to advise the CC on study materials and conduct. The CAB represents an avenue to collect participant and family stakeholder perspectives in research devoted to the AsA and NHPI communities and will inform the CC on strategies to recruit and retain participants, feasibility of the protocol, language discordance, website and newsletter design, community engagement events, and data dissemination to communities. The CAB may be consulted to help with development of new research proposals and may participate in committees as needed. An innovative component of this proposal is that we additionally intend for the CAB to advise the CC on an ongoing basis regarding culturally sensitive approaches to modern data handling with respect to data security, privacy, and sovereignty. It will include members from the Asian American, Native Hawaiian, and Pacific Islander communities, and it will meet with CC leadership at least every other month. The CC will be responsible for all administrative details concerning the CAB. We intend to utilize the outreach approaches of the CCET at the Utah CTSI to develop the criteria for membership on and appointment to the CAB. The CCET has experience recruiting CAB membership from around the U.S., enabled by the rise of virtual meeting technologies spurred by the COVID-19 pandemic. We plan to recruit membership from across the U.S. that will focus on the geographic locations of

the CC, CCFCs, and any partner organizations. The process whereby CCET identifies participants for community engagement activities is described fully in Section E in *Facilities and Other Resources*. We will specifically seek some members who express interest or have expertise in modern approaches to data handling.

B.1.10 Ad hoc Committees

Ad hoc committees may be formed at the discretion of the SC. These are intended for specific, time-limited purposes. There will be two such committees established at the initiation of the network: the Manual of Operations Committee and the Performance Metrics Committee.

- The *Manual of Operations Committee* will draft the AsA-NHPI Cohort Study Manual of Operations, which includes Standard Operating Procedures. After the Manual is approved by the SC, this committee will be dissolved.
- The *Performance Metrics Committee* will develop criteria and report-cards of site and CC performance metrics within the first three to six months after the protocol is finalized. The SC will approve the metrics. The purpose of metrics reporting is to assure that the goals of the network are realized. Performance metrics are likely to evolve to address new risks during study implementation. The performance reports will be made available within the network and to NHLBI staff via the secure Tableau reporting system described in *Facilities and Other Resources*. These reports will not be anonymized, as this allows sites that have opportunities for improvement to contact better-performing sites for assistance. None of these reports will be accessible outside of the network NHLBI and other Institutes and Centers.

B.1.11 Data Book Working Group

The Data Book Working Group (WG) is comprised of investigators and staff from the CC, CCFCs, and NIH who are interested in data dissemination via the data book. This WG is charged with advising the CC on the design of and content for the data book at the conclusion of the study. It is anticipated that Dr. VanBuren (MPI) will participate in the data book WG, along with other members of the CC staff who are integral to the design of the database, such as clinical data managers and statisticians.

B.1.12 Mental Health Working Group

The Mental Health WG is comprised of investigators and staff from the CC, CCFCs, and NIH who are dedicated to the safe collection and maintenance of the mental health instruments and outcome assessments. It is anticipated that Dr. Baucom (Co-I) will participate in this WG, potentially acting as chair, to drive the needs of the mental health component of the AsA-NHPI Cohort Study.

B.1.13 Environmental & Lung Disease Working Group

The Environmental & Lung Disease WG is comprised of investigators and staff from the CC, CCFCs, and NIH who are dedicated to issues regarding environmental factors, particularly as they impact lung disease. It is anticipated that Drs. Zhang and Sward (Co-I) will participate in this WG.

B.1.14 Ad hoc Working Groups

Ad hoc WGs may be formed at the discretion of the SC. These are intended for specific, time-limited purposes. For example, were the AsA-NHPI Cohort Study ongoing during the start of the COVID-19 pandemic, the formation of a COVID Working Group would be sensible. The Utah DCC can agilely implement database changes in response to urgent public health or societal threats that may be of interest to the AsA-NHPI Cohort Study investigators or the community. Dr. VanBuren will act as the CC liaison to any ad hoc WG that is formed that recommends study database changes or new instrument collection.

C Ancillary Study Development

The AsA-NHPI Cohort Study network may establish a process to develop research projects beyond the cohort study planned, potentially including interventional trials and meaningful translational and descriptive studies. In order to secure peer-reviewed funding for additional research, it is important to have a robust process for the development of scientifically rigorous, significant, and innovative grant proposals. The process proposed here is managed by the Ancillary Study Committee and uses several of the previously described committees (Figure 2). We have successfully implemented this proposed process in other established networks which results in approximately 70% funding rate when grants are submitted to the NIH, but the steps and approval thresholds will be revised in collaboration with the SC during the startup phase.

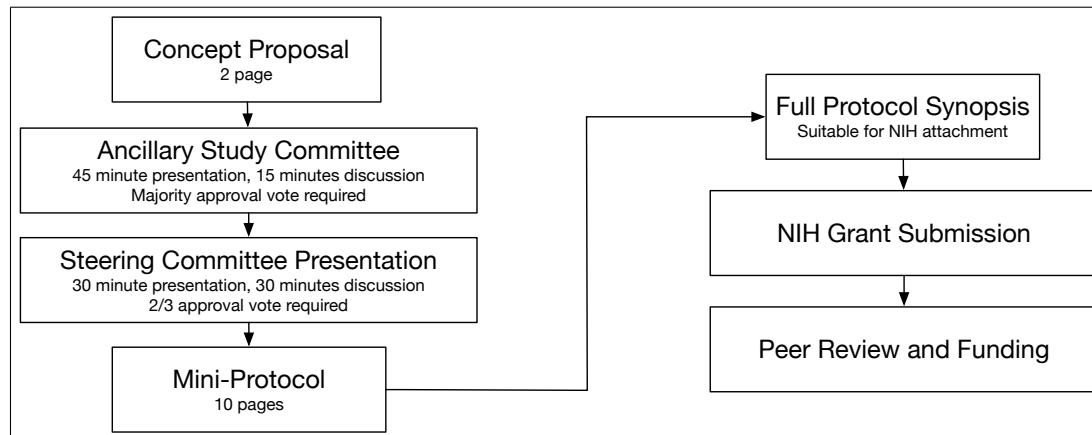


Figure 2: Process for Development of Additional AsA-NHPI Cohort Study Peer-Reviewed Research

Concept proposals are intentionally short so that an investigator can introduce an innovative research idea without major investment of time. After review and majority approval by the Ancillary Study Committee, the SC must approve the concept by a 2/3 vote in order for the concept to proceed further. Approved concepts are developed into mini-protocols in consultation with the Protocol Design and Review Committee. In parallel, the Protocol Budget Committee will assist the investigators to develop a feasible project budget. It is expected that this will be accomplished within three months of concept presentation. The mini-protocol will be presented to the SC by the investigator; the Protocol Budget Committee will present its budget recommendations prior to the SC voting whether to approve the mini-protocol to proceed further. For this vote (mini-protocol phase vote), a majority is sufficient.

Current NIH funding mechanisms for clinical research require the *Protection of Human Subjects* form. This form requires numerous attachments, including a protocol synopsis. The protocol synopsis will be submitted to the SC. The SC must approve the protocol synopsis by majority vote prior to submission of the grant to the NIH or other funding agency. It is not necessary for the entire grant proposal to be reviewed by the SC.

The process described here can require a significant amount of calendar time and is not suitable if there are special funding opportunities that might arise for rapid initiation of studies with high public health significance, exemplified by the COVID-19 pandemic. These opportunities usually have very short timelines for development and submission of applications. In order to enable such research in the AsA-NHPI Cohort Study network, investigators may present their concept to the SC, and after approval, the grant proposal may be assembled without further SC presentations or votes (i.e., skip the protocol vote step). The investigators have access to the expertise of the Protocol Design and Review Committee and Protocol Budget Committee, as well as the SC. The grant proposal, including protocol synopsis and budget, must be reviewed and approved by the SC prior to submission to the NIH. This accelerated mechanism will not be applicable if submission dates are greater than 120 days after a funding announcement is released.

All AsA-NHPI projects (including these Ancillary studies) will adhere to the *Resource Sharing Plan* that is included with this application. The CC is fully committed to making resources available to non-network investigators to make good use of the data that will be collected in this important study.

Specific Aims

Approximately 7.7% of the United States population are self-reported Asian American (AsA), Native Hawaiian, or Pacific Islander (NHPI). AsA and NHPI include over 40 culturally distinct race and ethnic groups. Yet, these populations are typically aggregated in population research. Inappropriate aggregation obscures health disparities in these communities since many chronic health conditions differ among the groups. An NHLBI workshop on research opportunities for AsA and NHPI health resulted in a report detailing population research gaps. The report recommended the development of an infrastructure to serve as a platform to collaborate, coordinate, and implement innovative research in AsA and NHPI populations. This infrastructure aims to aid understanding of sociocultural, environmental, psychological health, and lifestyle dimensions, in addition to quantifying and evaluating metabolic, cardiovascular, lung, cancer, and aging diseases in AsA and NHPI communities.

The University of Utah Data Coordinating Center (DCC) is responding to RFA-HL-23-016 to be the Coordinating Center (CC) for a new AsA-NHPI epidemiological cohort study to address this population research gap. Other institutions will respond to be the Clinical/Community Field Centers (CCFC). The Utah DCC is uniquely qualified to serve as the CC. The Utah DCC has successfully coordinated, developed, and analyzed >140 studies over the last 20 years including cohorts and observational data sets respecting data sovereignty in diverse populations. The Multiple Principal Investigators Drs. Dwyer, VanBuren, and Raphael provide internationally recognized leadership. Dr. Dwyer, the director of the Utah DCC, is an international leader in clinical trials. Dr. VanBuren provides sophisticated biostatistical leadership and successfully manages multiple networks and studies. Dr. Raphael, a Native Hawaiian, is a clinical and translational scientist, community activist, and leader who provides culturally sensitive context to the CC efforts and deep connections to the NHPI population.

The Utah DCC intends to provide overall management, coordination, communication, leadership, and support of the AsA-NHPI Cohort Study across the entirety of the program. The development and piloting of enrollment using a single protocol across all the sites during the UG3 phase is critical to ensure successful transition to the UH3 phase. The Utah DCC is well positioned to successfully navigate the network through the UG3 phase to develop and finalize a valid and implementable study protocol. We have the existing infrastructure to *immediately* implement the following Specific Aims that correspond to 1) network setup and protocol development (UG3 Phase), 2) study implementation (UH3 Phase), and 3) analyses and dissemination of data (UH3 Phase):

Specific Aim 1. Coordinate with the CCFCs and the Project Officers to provide *independent* clinical and biostatistical leadership and expertise to establish the culturally sensitive network infrastructure with key cross-study committees, develop necessary materials including the protocol/training plans and data collection tools, and direct the logistics of site capitated payments for data/biospecimen collection.

Specific Aim 2. Collect and harmonize phenotypic data using common data elements and standardized assessments utilizing our existing DCC infrastructure to ensure data integrity, security, and sovereignty of collected populomic data, including biospecimens via a dedicated central laboratory and biorepository.

Specific Aim 3. Provide an analytical and dissemination infrastructure, including implementing processes for timely data analyses, tracking publications, assisting with future funding opportunities, and managing outward-facing materials such as a public/participant and investigator website, data book, newsletter, and public-use dataset suitable for deposit in NHLBI repositories.

The Utah DCC has played a crucial leadership role during the establishment and maintenance of all our networks and projects. Clinical and biostatistical expertise at every stage of study development and implementation have enabled efficient designs and organization to maximize productivity. State-of-the-art information technology has enabled efficient communication and protection of highly sensitive data. We believe the top priority of the CC is to facilitate the development of a protocol by the Steering Committee to enable the transition from the UG3 to UH3 phase. Our track record demonstrates our ability to successfully implement these aims utilizing existing infrastructure.

We will collaborate fully in all AsA-NHPI Cohort Study functions, working with the Steering Committee, CCFCs, and NIH Staff under the Cooperative Agreement mechanism. We fully understand, accept, and support the participatory and cooperative nature of the collaborative research process required in multicenter research.

Research Strategy

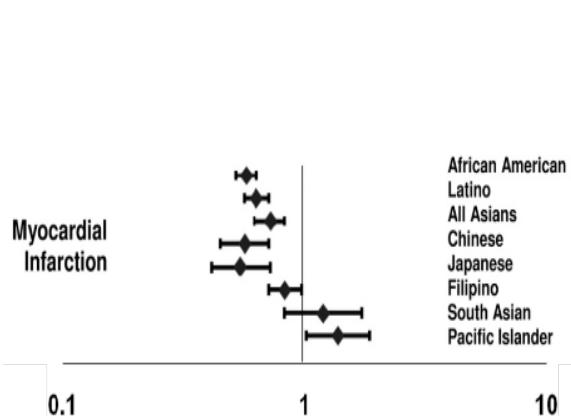
A Significance

According to the 2020 US Census, 6.2% (20.6 million) of the US population self-identified as Asian American (AsA), Native Hawaiian, or Pacific Islander (NHPI) race alone²¹⁸ and another 5 million individuals self-identified as AsA or NHPI in combination with another race. Despite a significant presence in the US, individuals from these communities are vastly underrepresented in large cohorts such as the Framingham Heart Study, the National Health and Nutrition Examination Survey (NHANES), and the National Health Information Survey (NHIS). Administrative claims data sets, such as Medicare, Medicaid, TriNetX, and Optum Clininformatics® Data Mart, are frequently used to report health information by race and ethnicity. However, the reliability of race and ethnicity data for AsA and NHPI in administrative data sets is questionable. The Medicare administrative dataset consistently undercounts AsA and NHPI,²¹⁹ and commercial administrative datasets use unvalidated approaches to categorize race and ethnicity.²²⁰ According to the 2020 US Census, Utah ranks third (1.8%) behind Hawai'i (27.1%) and Alaska (2.5%) in terms of proportion of the population that is NHPI. This connection affords us the opportunity to engage the NHPI community as an advisor to the CC in this cohort study.

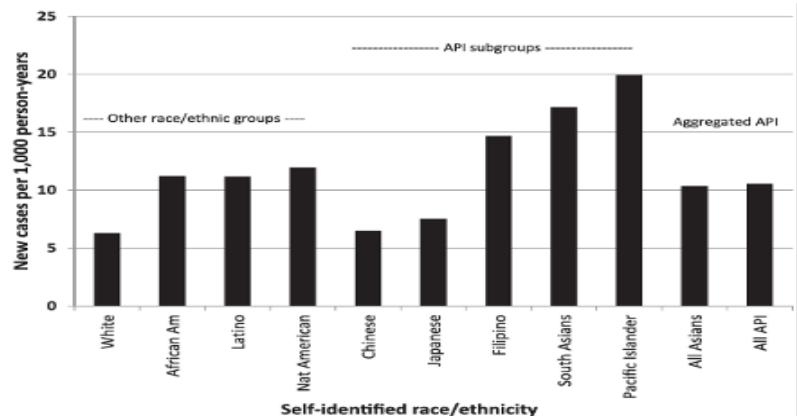
A.1 Historical Representation of the AsA and NHPI Communities

When available, AsA and NHPI data are often aggregated. Inappropriate aggregation obscures health disparities in these communities because it does not accurately characterize the health of AsA and NHPI. Further, AsA, NHPI, and populations within these overarching categories are genetically and ethnically diverse, have different social and cultural norms, and have different lived experiences in the US. Some populations have had difficult relationships with the US as well. Native Hawaiians still resent the illegal overthrow of the Kingdom of Hawai'i by the US in 1893, and nuclear testing in the Marshall Islands has led to high rates of cancer in Marshallese individuals. Aggregation of AsA and NHPI data is particularly problematic for NHPI because they are vastly outnumbered by Asians in the US. Of the 20.6 million Asian, Native Hawaiian, or Pacific Islander race alone, only 690,000 (3.3%) of these are Native Hawaiian or Pacific Islander. Disaggregation of AsA and NHPI data in Northern Californians with diabetes revealed that Pacific Islanders were the only racial and ethnic group to have a statistically significantly higher risk of myocardial infarction than Whites (Figure 1a).²²¹

In the same cohort, disparate incidence rates of diabetes were observed within AsA (higher among Filipinos and South Asians than Chinese/Japanese), and Pacific Islanders were found to have the highest diabetes incidence rates of all racial and ethnic groups, a finding that would have been masked without disaggregation (Figure 1b).²²²



(a) Hazard ratios of MI in Northern Californians with diabetes by race and ethnicity (v. White race)



(b) Standardized diabetes incidence rates (per 1000 person-years) by self-reported race and ethnicity in Northern Californians with diabetes.

Figure 1: Data from a Northern California cohort study.

For these reasons, it is critical to capture even more granular race and ethnicity data than simply AsA or NHPI. In addition to masking disparities within AsA and NHPI populations, including the communities that comprise AsA and NHPI, data aggregation also creates a false sense of visibility for NHPI communities who very much feel invisible. It remains disappointing that high-impact American medical journals permit aggregation of Asians and Pacific Islanders in guidance on the reporting of race and ethnicity.²²³

A.2 Community-Informed Needs Assessment

The AsA-NHPI Cohort Study is a critical step to better characterize the health status and resiliency of these populations. Engaging AsA and NHPI in research projects is notoriously challenging owing to a variety of factors including language discordance, mistrust of the medical community, lack of early and ongoing engagement, and concerns regarding data privacy, security, access, and sovereignty.^{224,225} It is critically important for this novel cohort study to be informed by culturally responsible approaches to study design, participant enrollment and retention, collection of sensitive information including DNA, and modern data handling. In anticipation of this submission, we conducted a listening session arranged by University of Utah's Community Collaboration & Engagement Team (CCET) to obtain community feedback about conducting a large cohort study in AsA and NHPI. Seven individuals from Japanese, Pakistani, East Indian, Filipino, Samoan, Tongan, and Native Hawaiian communities participated. The mean \pm SD age was 43 \pm 11 years with 6 women. Common themes included the following:

- Enthusiasm for this study and how it can help their children, grandchildren, and community members
- Community members should have meaningful input into the study design and execution
- Recruitment will be more successful in community settings (churches, mosques, festivals, etc.) than in clinical environments due to a perceived imbalance of power in the clinic
- Most were comfortable with modern techniques of storing and de-identifying data
- Importance of sharing data with participants and communities during the study, and strategies to do so such as web-based or smartphone applications, community events, and newsletters
- Willing to provide DNA; some want DNA destroyed if not analyzed quickly (e.g., 3 years).

Based on this community feedback, we anticipate that the Community Advisory Board (CAB) will advise the AsA-NHPI Cohort Study on practices regarding community engagement, data acquisition, data collection, and data dissemination via website and/or mobile applications, and newsletter. The CAB will provide feedback regarding the feasibility of the protocol assessments, the language and tone of the protocol and participant-facing documents, newsletters, the website, participant engagement, recruitment/retention, and culturally sensitive approaches to modern data handling with respect to data security, privacy, and sovereignty. We have budgeted for necessary translation of participant-facing documents throughout the course of the project. The CAB may be consulted to help with development of new research proposals and may participate in committees as needed. The organization of the CAB are fully described in *Overall Structure of the Study Team*.

B Innovation

B.1 Community Connections

As a result of the strong ties of the University of Utah to the NHPI and AsA communities, we are uniquely positioned to effectively partner with an otherwise hard-to-reach population. Our planned CAB for the CC will be recruited from membership across the U.S. that will focus on the geographic locations of the CC, CCFCs, and any partner organizations, thereby making the CAB representative of participating locations involved in this project. We are proposing to include members on the CAB with a special interest or expertise in data governance. The CAB will meet with the CC on a regular basis and will provide input on data issues such as data handling with respect to data security, privacy, sovereignty, and weaponization. The CAB is described in more detail in *Overall Structure of the Study Team*.

B.2 Flexibility and Agility in Data Collection Methods

Analogous to personalized medicine for patient care, we believe data capture methods should be customized to each site. While a central set of data elements will be collected at all CCFCs, an innovative feature of our application is the customized method of collection across sites. The Utah DCC has expertise across the entire spectrum of data collection methods, from 100% manual data entry to fully automated data transfers. In a typical study, a single method is prescribed to enrolling sites. For a study of this magnitude, we intend to allow for each CCFC to customize the level of “automation” of participant data transfer that meets the needs of the CCFC. Once automated techniques are established, the ability to increase participant enrollment becomes increasingly simpler, with minimal extra effort required by the CC.

In addition to flexibility of data collection methods, it is critical that modern cohort studies are agile in their ability to collect data other than originally proposed. Coordinating centers must be capable of collecting participant responses to social, societal, environmental, and other changes quickly and efficiently. Using the COVID-19 pandemic as an example, it is beneficial for an ongoing cohort study to query participants regarding healthcare utilization, working conditions, and family impact to quantify the effect of COVID-19 in the population, e.g., the effect of anti-Asian sentiment on the mental health of AsA community members. In order to successfully implement this process, the CC must have the capability and flexibility to add data fields as soon as requested. **The Utah DCC has the ability to incorporate and implement changes to the database within 1 business day of the finalization of the data form.** As described in the MPI plan, Dr. VanBuren will oversee all data collection and will ensure these change requests are immediately prioritized and successfully implemented.

B.3 Digital Health

We plan to use Digital Health to collect direct participant communication (e.g., texting, image uploads), wearable data, and sensor data, depending on the needs of the AsA-NHPI Cohort Study and data planned to be collected. In a study of children with Lyme meningitis, coordinated by MPI Dr. VanBuren at the Utah DCC, parents of study participants text images of their child's facial palsy to the DCC. After each image is uploaded, an automatic notification is sent to a research coordinator within the Utah DCC to review the images for suitability for the study. If the image is unusable, the coordinator manages the process to contact the participant to recapture a suitable image. Once the image is deemed acceptable, the images are reviewed by a central neurologist in a process managed by us. In the Pediatric Research Using Integrated Sensor Monitoring Systems (PRISMS) study coordinated by Co-Investigator Dr. Sward, data were collected from environmental and wearable sensors which were integrated with app and clinical electronic health record (EHR) data to implement automated home interventions (e.g., automatically turning on a fan in response to increased particulates). We have streamlined the process of Electronic Patient Reported Outcomes (ePRO) and Electronic Clinical Outcome Assessments (eCOA) collection and intend to bring these capabilities to this AsA-NHPI Cohort Study.

B.4 Participant-Facing Data

In most large-scale multi-center research, the data collected are not returned in a usable way to the participants and the communities studied. Typically, public-use datasets (PUD) are generated which require access to the data and the ability to manipulate specific data files and types. We believe participants invest themselves in a study when they understand and visualize the impact their individual data has on the knowledge generated from the study. As discussed in Section G of the *Cohort Management Plan*, our public-facing website will have interactive features allowing for both investigators and participants to explore relationships in the data, spur hypotheses, and infer conclusions.

In addition to the public-facing website and the data book, we anticipate production of a one-to-two page, “Where do I stand in the AsA-NHPI Cohort” document for each participant. This document will be generated at the CC annually after enough participants are enrolled in the AsA-NHPI Cohort Study (e.g., 500 participants). This document will display demographics, labs, and select data elements from collected instruments. The research coordinator at the CCFC will download the document, review the data with the PI, and then offer to deliver it to the participant if they have agreed to receive it. This ensures the participant does not receive clinical information that is new to them. In the interest of privacy, the CC will report the participant’s data but display it via specific

quantiles, which will be determined in consultation with the appropriate committees.

B.5 Novel Study Design

While this study is focused on the development and maintenance of the AsA-NHPI Cohort Study, we expect future funding opportunities will catalyze investigation of the rich dataset collected. The Utah DCC has extensive experience implementing novel study designs and analyses (e.g., Bayesian adaptive designs, probabilistic linkage of databases) across a variety of networks as described in Section A of *Facilities and Other Resources*. We will bring this experience to the AsA-NHPI Cohort Study when future funding is considered. We have the capability to scale up to 10 additional research projects per year in this network.

B.6 Creation of Study Materials

In multi-center research, a critical aspect of study startup is the speed in creating documents and ensuring consistency of those documents across sites, including version control. Platforms that help us achieve these aspects are fully described in *Facilities and Other Resources* and include Consent Builder and L^AT_EX. Consent Builder is a software platform created and maintained by the Utah DCC that allows for automatic creation of consistent yet unique site consent forms. Overall study and site-specific language are entered into the software package and IRB-templated consent forms are automatically populated.²²⁶ The Utah DCC uses L^AT_EX, a sophisticated typesetting software platform that automatically produces a properly formatted protocol and Manual of Operations. We have readily available templates for language regarding Human Research Protection, adverse event collection, outcome evaluation, and CC infrastructure, all of which reduce the need for recreation.

C Approach

C.1 Specific Aim One

Specific Aim 1. Coordinate with the CCFCs and the Project Officers to provide *independent* clinical and biostatistical leadership and expertise to establish the culturally sensitive network infrastructure with key cross-study committees, develop necessary materials including the protocol/training plans and data collection tools, and direct the logistics of site capitated payments for data/biospecimen collection.

C.1.1 Independent Clinical and Biostatistical Leadership

We believe that a combination of leadership expertise—both clinical and biostatistical—enables the CC to communicate most effectively with network investigators during protocol development (in the UG3 phase) and implementation (in the UH3 phase) because of domain familiarity. We have established a diverse clinical and biostatistical team on this proposal that covers many domains:

- Dr. Jamie Dwyer: multi-center research, data and clinical coordinating center operations, cardiovascular outcomes, chronic kidney disease progression
- Dr. Kalani Raphael: health disparities in NHPI communities, chronic kidney disease
- Dr. John VanBuren: multi-center research, network setup and maintenance, data and clinical coordinating center operations, novel study designs, statistical analysis
- Dr. Kathy Sward: nursing, common data elements, informatics, multi-center research, sensors/mobile apps, environmental data
- Dr. Brian Baucom: data coordinating center operations, mental health instruments, common data elements, sensor data
- Dr. Christy Porucznik: recruitment, retention, community-based cohort studies, mentorship of coordinators, biospecimen collection (logistical implementation)
- Dr. Yue Zhang: statistical analysis of environmental factors relating to lung and mental health
- Dr. Kevin Shah: cardiovascular outcomes, health disparities in AsA communities

We have found that CC clinical leaders are better able to understand subtle clinical issues during protocol development; it is sometimes difficult for a Ph.D. statistician to detect clinical flaws in study protocols and effectively

“push back” against investigators. The situation expands in difficulty and complexity when the CC also maintains responsibility for site performance monitoring and assuring regulatory compliance during a study. In this case, clinical expertise (nursing or medical) and community engagement expertise are almost always needed for effective communication and realistic expectations of site performance. Similarly, biostatistical leadership is critical in study startup and implementation to ensure appropriate processes are used to limit bias in data collection and analyses. **The combination of clinical and biostatistical expertise provides the robust leadership team necessary to successfully implement a complex project such as the AsA-NHPI Cohort Study.**

Independent leadership is a critical feature of our application. Our proposal and team members are not associated with any enrolling CCFC and there is no conflict of interest, which is necessary in the event that we must remediate problems at a CCFC or suspend enrollment.

C.1.2 Key Cross-Study Committees

As introduced in the *Cohort Management Plan* and expanded upon in the *Overall Structure of Study Team* required attachments, we propose several committees that we will establish and implement in the AsA-NHPI Cohort Study and future ancillary studies. Because we detail each committee in those attachments, we summarize our approach here. At the inaugural SC meetings, we intend to introduce and describe the purpose of our proposed committees. We have emulated our prior success in past networks as an example for committee integration within the overall AsA-NHPI Cohort Study network. After these presentations, the SC will officially create each committee as conceived. Appropriate personnel are then assigned to the various committees, and each committee will be responsible for drafting a 2-3 page charter describing their makeup, processes, and deliverables. The Utah DCC maintains multiple committee charters that will be used as a starting point. An overall manual describing the network and the various committees will be created by the CC and approved by the Steering Committee.

C.1.3 Study Materials

- *Protocol Development:* Excellent protocol development and study planning can eliminate numerous future points of failure. The study protocol should be understood and easily read and interpreted by CCFC investigators and research coordinators, since readability is important to later protocol adherence. Study workflow should be developed in conjunction with coordinators and investigators because complex workflows endanger the collection of valid and accurate data. Verifying that all outcomes are crystal clear to research staff at multiple sites will eliminate many misunderstandings later in the study. After investigators provide feedback in the protocol, the Observational and Safety Monitoring Board (OSMB) and NIH program officers will review, edit, and approve the protocol prior to initial IRB submission. **To streamline the process of protocol creation, we have created an outline of key protocol considerations in Section C.1.4 for the AsA-NHPI Cohort Study informed by previously funded NHLBI cohort study protocols.**
- *Training Material:* Study training is critical for both investigators and research coordinators to implement a study of this magnitude. In studies coordinated by the Utah DCC, we usually host a 2-3 full-day training where the entire workflow, database, Good Clinical Practice (GCP), Good Laboratory Practice (GLP), Biospecimens, and other study aspects are discussed. During training we utilize interactive components to engage study teams, which solidifies the overall understanding of the protocol. For example, if a study has complex entry criteria, we create vignettes of plausible patient characteristics and have the sites evaluate if the individual is truly eligible. In a recent study that has an extensive laboratory component requiring central processing (as required by this study), we brought blood, pipettes, and centrifuges to the training. Research coordinators and investigators practiced the novel laboratory procedures, and the study Principal Investigator (PI) ensured samples were appropriately processed. In-person training is supplemented by online training that occurs pre-enrollment AND during enrollment. Regular training during enrollment reinforces critical study aspects and improves the quality of the overall study. We describe our online training system in the *Facilities and Other Resources*.
- *Manual of Operations:* In each of our conducted studies, we draft the Manual of Operations (MOO) that describes details of study conduct not appropriate for the protocol. This document is drafted by the CC Project Managers (PM), viewed through the lens of what a research coordinator needs to know in order to successfully implement the study. The MOO describes a breakdown of workflow and details complex

procedures. The PMs begin by note-taking and outlining the MOO starting at the initial kickoff meeting and continue by drafting language based on learnings from each PI call. We have found that the pain-points are typically the areas of confusion that deserve their own sections within the MOO.

- **Risk-Based Monitoring Plan:** As outlined in the *Cohort Management Plan* describing training and monitoring of study sites and staff, the Utah DCC has a robust risk-based assessment and monitoring approach based on the ICH GCP E6 R2 guidelines. Risk assessment and mitigation strategies are an important way to prospectively identify innovative steps to improve the likelihood of a successful trial. Risk assessments should focus on study specific risks, not the generic risks encountered in all studies (such as data entry error and missing data). In a recent trial of older adults with hydrocephalus with a gait test as the primary outcome assessment, we recognized that site personnel would not be able to consistently analyze and interpret the tests. We prospectively decided to videotape all gait assessments to mitigate this risk. Recordings would be evaluated by a third party within a week, and we were able to identify on-going variances and correct them in near-real time. This helped assure that the primary outcome data were accurate and consistent throughout the sites. The CC study team will work collaboratively with site investigators to identify unique risks to the AsA-NHPI Cohort Study. CC members will then ‘de-risk the protocol’, if possible, and produce processes to help mitigate and monitor the risks. Reports are created of identified risks and metrics quantifying the risks are regularly shown to investigators on PI calls. We have started the risk assessment process for the AsA-NHPI Cohort Study, and we outline initial identified risks and our current mitigation plans in Table 1.

Table 1: Identified Risks to the AsA-NHPI Cohort Study

| Risk | Reasons for Risk | Mitigation Plans |
|-------------------------|--|---|
| Low enrollment | <ul style="list-style-type: none"> · Data collected are culturally insensitive · Community does not fully support the study | The CAB will have representation from the communities surrounding the CC and each CCFC. Participant-facing documents will be pilot tested with the CAB to ensure appropriate terminology. Prior to the Pilot Phase of the UG3, the CC will discuss data collection with the CAB. |
| Loss to follow-up | <ul style="list-style-type: none"> · Intensity of participant involvement is burdensome · No direct benefit to participants · Loss of legitimacy of the study, from the participants’ perspective | The CC CAB will pilot collection of assessments and provide feedback on which of them are labor intensive. The CC will produce public-facing dashboards in addition to reports with the participant’s own data to encourage ongoing involvement. The CAB will provide ongoing guidance regarding potential risks to legitimacy of the study and mitigation plans. |
| Refusal to collect data | <ul style="list-style-type: none"> · Distrust of genomic material collection · Individuals may express discomfort at some assessments (e.g., mental health, religiosity) | The CAB will provide iterative feedback on drafts of participant-facing forms to ensure appropriate language is used to explain the importance of the collection of genomic material and sensitive assessments. |
| Unbalanced enrollment | <ul style="list-style-type: none"> · Under-representation of some Asian American, Native Hawaiian, or Pacific Islander populations | The CC will propose to the SC prior to study start potential enrollment caps to ensure populations are sufficiently enrolled. Enrollment reports will regularly summarize the current number of each enrolled population. |

C.1.4 Proposed Study Protocol Key Considerations

Overall Study Design, Sample Size, and Duration The full protocol will be developed during the UG3 phase. It is the top priority of the CC to successfully facilitate the development of the protocol and the transition from the UG3 phase to the UH3 phase. The number of participants is 10,000, which will include 4 to 5 major populations within AsA and NHPI. To improve understanding of human genetic variation, 25% of the population will include AsA and NHPI who are among the most understudied in biomedical research. Specific details outlined in the RFA are not repeated here.

Recruitment, Informed Consent, and Screening Individuals will be recruited by CCFC personnel and informed consent will be obtained prior to scheduling the baseline visit. Potential participants will be screened at the Screening Visit to determine their eligibility to participate in the AsA-NHPI Cohort Study.

Visits and Assessments Visits may be conducted in the clinics, the field, the home, remotely, or other location suitable to the participant and the CCFCs.

- **Baseline Visit and Exam, V1.** Assessments proposed to be performed at Baseline include questionnaires to collect granular race and ethnic group information (e.g., Palauan, Samoan), including the option of multi-race reporting; questionnaires on acculturation, discrimination, social networks, and residential history; medical and personal histories including smoking, current medications, sleep and respiratory symptoms,

sociocultural and environmental influences, lifestyle dimensions (diet and exercise), and psychological and cognitive health; assessment of body weight/height, blood pressure, pulse; electrocardiogram (ECG); spirometry; phlebotomy and random urine collection. *Laboratory tests* to be performed at V1 include chemistry panel including liver function tests, hemoglobin A1c (HbA1c), lipids, including direct measurement of LDL, lipoprotein(a) (Lp(a)), homocysteine, high-sensitivity troponin T, 5th generation (cTnT), high-sensitivity CRP (hsCRP), uric acid, CBC with platelets, and urine albumin:creatinine (UACR) ratio. Plasma, serum, and urine from V1 will be collected, and shipped to and stored by the Utah Biorepository. Blood samples will be collected at V1 using PAXgene technologies for genomic DNA and RNA. Toenail samples will be obtained for storage. We describe below proposed questionnaires and instruments.

- *Follow-up Visits.* We anticipate visits will occur every approximately every 6 months after the baseline visit. At these visits, questionnaires will assess for intercurrent life events, illnesses, hospitalizations, and other health events (e.g., emergency room visits, surgeries). Events that require adjudication will have clinical records collected for the Adjudication Committee. On the annual visits after baseline, we may additionally obtain spirometry, ECG, height, weight, blood pressure and heart rate, and blood and urine for storage in the biorepository. At the year 2 follow-up visit, we plan to repeat the laboratory tests performed at baseline and store blood and urine in the repository.

Proposed Questionnaires and Instruments We have produced a proposed list of assessments as a starting place for conversation with the Steering Committee. Iterative discussions will allow for the refinement (removal and addition of other assessments) of data elements.

- *Demographics:* WHO-DAS demography, including detailed racial and ethnic origin (with country of origin)
- *Functional Status or Impairment:* WHO-DAS domains (mobility, self-care, getting along with other people, life activities, participation, effects on difficulties)
- *Current Symptomology:* DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure—Adult, PROMIS Global Health or other profiles (e.g., PROMIS-29 or -43), Respiratory instruments (PROMIS Bank v1.0)
- *Mental Health and Cognition:* PHQ-9 (depression), GAD-7 (anxiety), NIH Toolbox Cognition Battery
- *Social Determinants of Health:* WHO-DAS Background (occupation, work status, etc.), AHC-HRSN main survey and supplemental measures (housing instability, food insecurity, transportation problems, financial strain, employment, community support, etc.)
- *Socio-cultural Factors:* WHOQOL-SRPB (spirituality, religion, personal beliefs), PROMIS measures Neuro-QoL Item Bank v1.0-Stigma, American Community Survey
- *Lifestyle and Behaviors:* PhenX (e.g., smoking, substance abuse), PhenX Nutrition domain, PhenX toolkit Physical Activity and Physical Fitness domain
- *Environmental Exposure and Geographic Influences:* residential history, census tract, rural-urban community area code, RECORD (neighborhood effects), air quality

C.1.5 Statistical Considerations

Cohort studies by nature are statistically complex due to the oversampling of populations in addition to the embedded nested relationship between observations. We know certain populations of the AsA and NHPI communities will be oversampled compared to the general distribution of these communities within the United States. This requires statistical corrections to make generalizable inferences. Dr. VanBuren has experience performing these corrections in a recently completed study of pediatric trauma patients where different injury profiles were oversampled for enrollment.²²⁷ In addition to the generalizability statistical adjustment, we must appropriately control for nested relationships. We anticipate enrollment of more than one family member within a household (e.g., siblings, cousins, different generations) and longitudinal measurements on each participant. Statistical techniques such as Generalized Estimating Equations and Mixed Effect Regressions can account for these correlations using complex correlation structures.

Individuals will likely be recruited via several methods. Statistically we can utilize census probability samples based on census tract data to identify potential participants similar to the process used for the National Health and Nutrition Examination Survey (NHANES).²²⁸ Briefly, this method samples in the following sequence: counties, census blocks within counties, households within census blocks, and finally individuals within households.

Stratified sampling can be performed where certain populations (e.g., Tongan) are oversampled to ensure inferences can be made with appropriate sample sizes. Weighting is used to produce generalizable inferences. CCFCs will be chosen by NHLBI so this sampling technique would begin at the census block stage. We believe low enrollment will be a risk to the study, so in addition to statistical sampling methods like that described above, we will encourage other techniques for enrollment. One method includes community outreach to local organizations that have connections to the populations of interest, and we will supplement community outreach with advertisement through social media.

Power calculations are unavailable because they will depend on which primary outcomes are selected by the Steering Committee. Towards the end of the pilot phase, sampling designs and power calculations will be performed to identify required sample sizes for the selected outcomes among populations to achieve certain confidence levels based on pilot data and historically known rates. Based on the RFA which describes 4-5 subpopulations among 10,000 participants, this suggests approximately 2,000 participants per subpopulation. If the natural event rate of an outcome (e.g., myocardial infarction) was 4%, one year's data on events for 2,000 participants would allow us to estimate the true event rate within $\pm 0.9\%$. Similar analyses will be performed based on the finalized number of expected follow-ups, number of subpopulations of interest, and outcomes of interest. Power calculations similar to this example will be performed based on defined outcomes, and the proposed enrollment capitations could be updated if so warranted by power calculations.

C.1.6 Contractual/Financial Management and Single Institutional Review Board (SIRB)

The Utah DCC has a designated contract specialist who manages data use agreements, business associate agreements, and contracts. Having implemented over a hundred unique studies with sites across the country, we have drafted our template contract language such that most sites have limited edits during legal negotiations. We will use these templates as starting points for contracting with sites. Both the Biorepository and Central Laboratory are affiliated with the University of Utah which streamlines the contracting for these entities (and reduces the number of contracts each site needs to have).

We will use the University of Utah Institutional Review Board (IRB) as the Single IRB (SIRB) of record. Utah has implemented over 130 SIRB projects and has streamlined the process for study and site navigation through the SIRB process. The Utah DCC project managers all have experience working through the Utah SIRB system (described in more detail in *Facilities and Other Resources*) and the IRB managers at the University of Utah have established relationships with most major academic research institution IRBs in the United States.

C.1.7 Observational and Safety Monitoring Board (OSMB)

The Observational and Safety Monitoring Board (OSMB) will be appointed in accordance with NHLBI policy and approval. The Utah DCC and Co-Is have extensive experience preparing for, implementing, participating on, and chairing safety monitoring boards, including Data and Safety Monitoring Boards (DSMB) in clinical trials and OSMB in observational studies. All Co-Is and MPIs have been involved with monitoring boards and will work with Dr. VanBuren in the setup and maintenance of the AsA-NHPI Cohort Study OSMB. We will use NHLBI OSMB's Charter template language as a starting point and will customize the OSMB Charter to fit the needs of this cohort study. We have experience organizing and leading all aspects of meetings (in-person, virtual, and hybrid), including minutes generation for the OSMB members to review, edit, and approve. Example material we expect to be included in the OSMB report include safety data, quality and completeness of study data, site performance, outcome event rates, and enrollment and retention information. Other sections will be incorporated as needed once the protocol is finalized in collaboration with the Steering Committee. Results will be presented overall and by identified subpopulations of interest. The OSMB will be involved throughout study startup and will approve the protocol prior to SIRB submission. We will ensure study leadership attends OSMB meetings and will plan meetings around the in-person SC meetings. We have budgeted for OSMB travel to a planned in-person meeting once a year. Supplemental virtual OSMB meetings will occur depending on the need.

C.1.8 Network Meetings

We plan for several in-person meetings with the CCFCs and NHLBI during the UG3 phase to draft all startup materials which includes the protocol. We believe in-person meetings are more productive than shorter virtual meetings. After transition to the UH3 phase, we are assuming there will be two in-person SC meetings a year during enrollment and one in-person SC meeting a year during follow-up which will be supplemented by monthly SC calls. Several of our networks have meetings in Washington, DC and the Utah DCC has experience making conference arrangements in this area.

C.1.9 Community Advisory Board

The CAB is introduced in Section B.1.9 in *Overall Structure of the Study Team*. The CC will have its own CAB and will coordinate the community engagement activities across the awarded CCFCs. We will develop the IRB application necessary to constitute the CC's CAB. We have this experience, since the MPIs and Co-Is have recently completed this process to develop our Needs Assessment for this proposal. We anticipate CAB meetings at least every other month, with the first meeting to be held in Fall 2023 during the UG3 phase.

C.1.10 Timeline Management

The Utah DCC has a Project Management Office (PMO) that provides a certified Project Management Professional (PMP) to each large study conducted by us. Most large projects in the Utah DCC utilize PMPs, and collaborating investigators now appreciate the multiplicative effects that missed tasks have for overall study startup. We will assign a PMP on Day 1 of the funding period to develop the timeline for startup of the AsA-NHPI Cohort Study. High-level Gantt charts will be a routine component of the CC's presentations to the SC. Our proposed timeline is found in *Timeline*, and the PMO is described in *Facilities and Other Resources*.

C.2 Specific Aim Two

Specific Aim 2. Collect and harmonize phenotypic data using common data elements and standardized assessments utilizing our existing DCC infrastructure to ensure data integrity, security, and sovereignty of collected populomic data, including biospecimens via a dedicated central laboratory and biorepository.

C.2.1 Common Data Elements

A common data element (CDE) is a standardized, precisely defined question that is paired with a set of specific allowable responses. Harmonized variable names and standardized coding rubrics (e.g., "0" = "no", "1" = "yes") are utilized to develop a CDE Detail file with structured representation of the instrument variables. While this study will ultimately have a unified set of data collected across all sites, we believe there may be initially several different data requests. We describe our proposed process to achieve the common set of data elements here. To harmonize data and implement common data elements, we use methods consistent with other pooled cohort studies. We begin with an intake process, examining each site's and NIH's proposed measures (as well as any data dictionaries that may be available from the sites). Metrics proposed by 2 or more sites are potentially targets for harmonization. We will compare site proposals with measures in the NHLBI Pooled Cohorts Study²²⁹ and other pooled cohorts such as ECHO.^{230,231} Measures from these cohorts that may be informative include smoking status, spirometry metrics and other clinical observations, representation of clinically relevant events, and environmental metrics. PROMIS measures^{232,233} are useful to streamline harmonization for relevant constructs, as may be measures from the PhenX toolkit.²³⁴ We anticipate that sites will collect and analyze race and ethnicity data in a granular manner, and will predetermine how to map these data onto OMB categories for race and ethnicity as required, starting from guidance by the Office of Minority Health.²³⁵ The AsA and NHPI communities are likely to recommend unique factors such as cultural information that is relevant for the community and we will likewise map this information onto OMB categories whenever possible.

Once a measure (survey instrument, ePRO, standardized observation, or other collection of variables) is identified for this cohort study, we categorize the measures. Typical categories might include core (required), supplemental (encouraged but not required), and site-specific (only collected at 1 site). We document metadata

including citations that support measure validation and information about copyright. We reconcile question verbiage, allowable responses, and response coding; documented in a 508-compliant²¹⁵ case report form (CRF). These structured representations are further linked (mapped) to existing NIH CDE²¹⁷ and where possible defined by standardized concept codes. For example, the GAD-2 question about how often a participant feels nervous, anxious, or on edge maps to the NIH CDE: m1ufksx5W, as well as to NCI thesaurus: C103565 and UMLS: C5197676 terms. The CC will ensure that permissions are obtained for use of validated measures. When an instrument or CDE does not exist in the CDE repository, we can submit the elements to the NLM. We have experience with the current (2022 August) submission template and are working in collaboration with NINDS and NLM staff to submit HEAL data elements. We are prepared to submit new elements from the AsA-NHPI Cohort Study in collaboration with NHLBI staff. Our team also has experience submitting questions to other standards organizations such as LOINC, should that be required.

The Clinical Data Managers utilize the CDE detail files as requirements specification, building the data capture forms based on the CDE specifications. Variable naming and response coding is verified by the statistics staff as part of the development of the statistical analysis plan, with strategy for transformations (such as aggregation for race variables) determined prospectively.

C.2.2 Data Collection

We will create the central database in our 21 CFR §11-compliant, validated instance of REDCap. Based on the protocol, our data managers create a Schedule of Events that outlines the participant flow and data collection at each timepoint or visit. Data managers work with research coordinators to ensure the proposed workflow appropriately mimics clinic workflow. The proposed data elements are mapped to one or more of the events which defines the structure of the database. After the data managers draft the database, an iterative process of review and refinement begins, starting with the CC staff, CC leadership and MPIs, CCFC research coordinators, and finally CCFC investigators. This process reduces database changes by identifying issues during the testing phase by all stakeholders. During this process, we encourage coordinators to enter a “plausible” participant they might encounter to ensure all choice options and skip-logic make sense.

As described in the *Cohort Management Plan*, we will offer each site the ability to automatically transfer data from the site’s EHR to the CC to reduce manual data entry. Once the database is moved to production, coordinators will enter the data that were designed for manual data entry as participants are enrolled. For direct database-to-participant contact (e.g., emailed surveys, texts, image uploads), we can customize the database to either automatically send the material request to the participant or for coordinators to manually push it to the participant.

C.2.3 Data Integrity

The Utah DCC will implement the AsA-NHPI Cohort Study utilizing our established infrastructure tools, methods, and processes to ensure data integrity. Within REDCap, data managers write automated checks that validate data during live data entry (e.g., a white blood cell count cannot be negative). Once data are submitted to the CC through REDCap, we utilize Query Manager (further described in *Facilities and Other Resources*) that performs complex cross-form discrepancy checks in the data warehouse. Queries are generated nightly from Query Manager to research coordinators on any discrepant data identified. We also write statistical checks that are related to items found in reports or OSMB materials. These automated checks catch the majority of data integrity issues, and they complement but do not replace site monitors. We utilize both in-person and remote site monitors who identify data integrity issues that cannot be automatically identified via the data alone. Our monitoring plan, including risk-based monitoring, is further described in the *Cohort Management Plan*.

C.2.4 Biospecimen Collection and Central Laboratory Data

In the *Biospecimen Plan*, we describe the specimens that will be collected for the Central Lab and Biorepository, how tracking of specimens is performed, how specimens and results are linked to the central database, and provide additional details regarding the capabilities and regulatory compliance of the Biorepository and Central Lab.

C.2.5 Site Performance Reporting

The Recruitment and Retention Committee will monitor recruitment and retention across sites. The Quality Committee will be responsible for evaluating all other site performance metrics (e.g., missingness of data, protocol deviations, number of outstanding queries, monitoring findings). The CC will develop and produce the reports necessary for Quality Committee oversight. An example from a current study coordinated by the Utah DCC illustrates our process for site performance reporting. In a cohort study of adults with scleroderma, MPI Dr. VanBuren presents monthly findings of data quality issues to the network's Quality Committee. He explains data concerns and provides potential solutions for the Quality Committee to consider. In addition to reporting to the Quality Committee, the CC will present high-level summaries of site performance on each SC call. We do not anonymize these reports which allows for CCFCs with opportunities for improvement to contact better-performing CCFCs for assistance. None of these reports summarizing site performance will be accessible outside of the AsA-NHPI Cohort Study CC, CCFCs, and NHLBI.

C.2.6 Recruitment and Retention

The Utah DCC has worked with enrolling sites in over 140 clinical research projects. We will draw upon the collective experience of Utah DCC staff, community advisors, investigators, study coordinators, and NIH staff to develop and implement a recruitment and retention plan. A proposed plan is provided in the *Recruitment and Retention Plan*. This plan addresses concerns raised during the community-based Needs Assessment we undertook to develop this proposal and describes highly customizable Utah DCC enrollment reports that are easily accessible to the CCFCs.

C.3 Specific Aim Three

Specific Aim 3. Provide an analytical and dissemination infrastructure, including implementing processes for timely data analyses, tracking publications, assisting with future funding opportunities, and managing outward-facing materials such as a public/participant and investigator website, data book, newsletter, and public-use dataset suitable for deposit in NHLBI repositories.

C.3.1 Data Analyses and Manuscript Processes

Data analyses will occur after data are collected, verified, and erroneous data are corrected. Since this is a cohort study, we recognize manuscripts will be written based on data available throughout the enrollment and follow-up process. This makes it critical to constantly have clean and reliable data. Recognizing that publishing study results is an important product of research, the Utah DCC has instituted an innovative process to assure the ability to publish the intended manuscripts in a timely manner. We intend to immediately implement this process for the AsA-NHPI Cohort Study with the Writing, Publications, and Presentations Committee, which is fully described in Section B.1.5 in *Overall Structure of the Study Team*. We begin with a "Manuscript Analysis Request Form" (MARF), in which the author outlines the anticipated tables and figures that will become part of the future publication. Our statisticians then create the "Manuscript Analysis Plan" (MAP) which fleshes out their understanding of the MARF contents. The goal is for the MARF → MAP process to occur as early as possible, preferably right as participant enrollment begins. This adds focus to the most important data elements assuring our team that all of the necessary data will actually be collected, and potentially eliminating data elements that will never be used. After the MAP has been finalized between the statistical team and the investigative team, the analytic scripts can be written *during* participant accrual. At the point when enough cohort participants are enrolled and manuscript data are locked for those participants, these scripts can be immediately executed, allowing authors of numerous papers to proceed with timely writing of the primary and secondary manuscripts. In a recently completed trial of probiotics intended to shorten the duration of pediatric gastroenteritis, the Utah DCC released the statistical analyses for 12 publications within four weeks of data lock, and all of those publications were written and published in a timely manner. During both Writing, Publications, and Presentations Committee and SC meetings, we will provide status updates on every manuscript in development to ensure complete visibility of data analyses and manuscript preparation. The CC will maintain a list of authors, credentials, affiliations, and emails to aid lead authors in the submission process for abstracts and manuscripts.

C.3.2 Future Funding Opportunities

In the *Cohort Management Plan and Overall Structure of the Study Team*, we describe the various committees that report to the Steering Committee (SC). We also describe the process for ancillary proposals to proceed from initial concept through grant submission. This mechanism described has achieved an approximately 70% funding rate for submitted applications in large networks coordinated by the Utah DCC. The Utah DCC has the capability to expand and move personnel onto ancillary projects as they are proposed and arise.

C.3.3 Dissemination Methods

We plan a variety of dissemination methods in addition to abstracts and manuscripts, and detailed information on the website, data book, newsletter, and PUD is found in *Facilities and Other Resources* and *Cohort Management Plan*.

- **Website:** The Utah DCC has designed and developed numerous websites to support networks, studies, and projects that serve as a resource for both public-facing and private uses. We embed Tableau dashboards to create a seamless experience for users for data exploration. We plan to create the AsA-NHPI Cohort Study website using our established infrastructure and processes. The CAB and Quality Committee will jointly determine what data should be accessible to the public, with final approval by the SC.
- **Data Book:** We currently maintain 3 data books in the Utah DCC. Dr. VanBuren has previously led the design and implementation of data books, and his experience will inform the CC's approach to the development of the Data Book for the AsA-NHPI Cohort Study. He will lead the CC in proposing content to the Data Book Working Group, which is fully described in Section B.1.11 in *Overall Structure of the Study Team*. Once the CC creates the mock template, we anticipate the SC will decide final content to be published.
- **Newsletter:** We currently manage multiple newsletters in networks coordinated by the Utah DCC, and content is developed in collaboration with the network PIs. We will translate the newsletter into relevant languages for the AsA-NHPI Cohort Study.
- **Public-Use Datasets:** The Utah DCC has streamlined the process for creating PUDs and has deposited 50 PUDs in various NIH repositories, including both raw and derived data. We commit to deposit all AsA-NHPI Cohort Study data in a PUD at the completion of the study and as needed when requested by NHLBI.
- **Social Media:** Ongoing dissemination of interim results via social media channels will encourage engagement of participants with the study. We plan to use the existing Utah DCC experience with social media to implement an AsA-NHPI Cohort Study social media presence, specifically Facebook and Twitter.

D Study Timeline

We outline and describe our proposed timeline for various activities in the UG3 and UH3 phases in *Timeline*. Here we show the proposed high-level timeline. The assigned PMP will finalize the project plan.

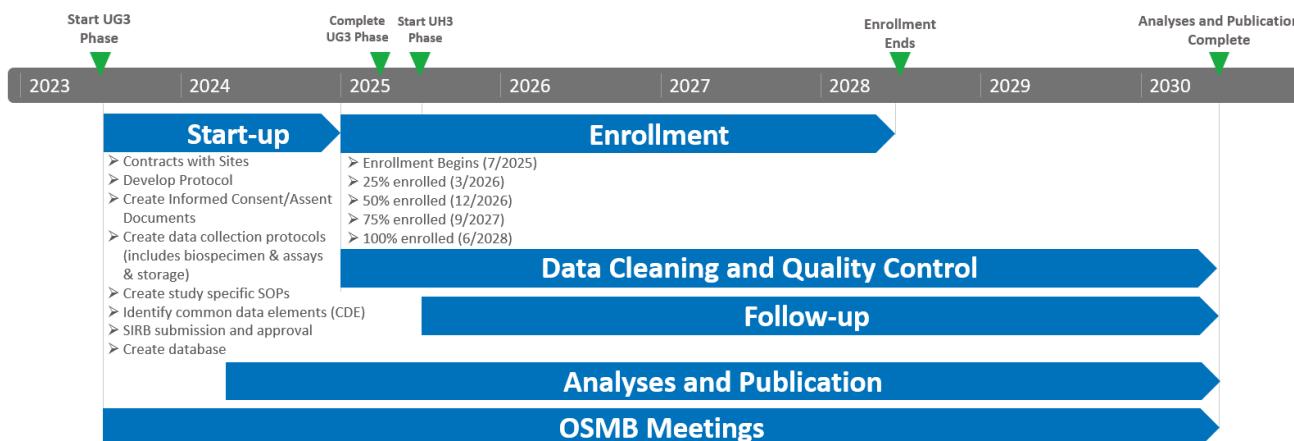


Figure 2: Condensed timeline for the proposed AsA-NHPI Cohort Study.

Multiple PD/PI Leadership Plan

Drs. Dwyer, Raphael, and VanBuren (MPIs) will provide oversight for all activities of the Utah Coordinating Center (CC) for the AsA-NHPI Cohort Study. They will be responsible for accomplishing the Specific Aims of the CC and ensuring that systems are in place to guarantee institutional compliance with applicable laws and DHHS and NIH policies including human participants research regulations.

The three MPIs will meet weekly, either by teleconference or in-person. The CC Co-Investigators and staff will join at least monthly to review the status and progress of all aspects of management of the cohort study. The MPIs will share responsibilities for allocating personnel resources as required. The cadence of meeting frequency for staff will be determined by the study needs but is anticipated to be at least weekly. The staff and CC structure are fully described in *Overall Structure of the Study Team*.

Dr. Dwyer will serve as contact PI and will assume fiscal and administrative management including maintaining coordination with the CCFCs, oversight of the budget, maintenance of staffing of the CC, and supervision of the Co-Is. He will coordinate protocol development, thereby ensuring the study stays in scope and successfully transitions from the UG3 to the UH3 phase. He will assume responsibility for communication with the NIH and annual reporting requirements.

Dr. Raphael will lead the CC's relationship with the Community Advisory Board (CAB) and oversee all community aspects of the study, thereby ensuring all materials (e.g., protocol, database) are culturally appropriate. Additionally, he will oversee recruitment and retention efforts, and ancillary study proposals and implementation.

Dr. VanBuren will be primarily responsible for overseeing data and statistical considerations and services as the protocol is developed during the UG3 phase. During the UH3 phase, he will oversee the day-to-day efforts of the CC and the generation of the data book. He will be the primary contact for the development of materials for the Observational and Safety Monitoring Board (OSMB). He will participate in all Ancillary Study proposal processes to ensure CC responsibilities are clearly delineated. Additionally, he will agilely coordinate the swift implementation of any database changes that may occur as a result of an urgent public health or societal threat about which the AsA-NHPI Cohort Study investigators may desire to collect data.

PI Succession Plan. It is not planned or anticipated that any of the MPI or Co-Investigators will leave the University of Utah. In the event that one of the MPIs leaves the institution, the CC function would remain at the University of Utah Data Coordinating Center (DCC), and one of the Co-I would assume more leadership roles in the overall day-to-day management of the AsA-NHPI Cohort Study CC. Dr. Sward, a Co-Investigator of this proposal, has deep, integrated experience in the Utah DCC and would be the appropriate choice.

Conflict Resolution. If a potential conflict develops, the MPIs will meet to resolve the dispute. If they fail to resolve the dispute, then the disagreement will be referred to the Associate Vice President for Research in Health Sciences, and the Vice Dean for Research in the School of Medicine, who shall resolve the dispute.

Letters of Support

1. VPR Erin Rothwell
2. AVPR Rachel Hess, for CCET, CTRC, CTSI
3. Pacific Islander Community
4. ARUP

Resource Sharing Plan

The University of Utah Data Coordinating Center (DCC) will provide immediate access to proven resources to accelerate the development, implementation, and evolution of the AsA-NHPI Cohort Study. Resource sharing/dissemination of data via the website is a key aspect of this proposal. Continued dissemination of resources will be impactful for the broader AsA and NHPI communities and investigators who wish to study these populations. Resources and innovations developed in collaboration with the CCFCs and NIH during the design and start-up of the AsA-NHPI Cohort Study are likely to have a sustained impact on the development and implementation of other future cohort studies, particularly in under-represented populations. Compliance with the resource sharing plan will be monitored and managed by the MPIs. Our *Resource Sharing Plan* outlined here adheres to the intent of the future Data Management and Sharing (DMS) policy (effective January 25, 2023) to promote the sharing of scientific data.

A Data Sharing Plan

A.1 Policies and Timing

Following completion of the AsA-NHPI Cohort Study in this proposal, the CC will prepare a final study database that is used for planned analyses (or more frequent if requested by NHLBI). The Writing, Publications, and Presentations Committee will prioritize the statistical analyses and publications. After the AsA-NHPI Cohort Study investigators have completed the publications planned for each study, or within one year (whichever is shorter), the CC will produce a completely de-identified dataset that can be used by investigators not originally part of the AsA-NHPI Cohort Study. The CC will also prepare an annotated packet of case report forms (CRF) (Figure 1) as well as a data dictionary that contains a concise definition of every data element included in the dataset. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. If a data element has been found to be unusable or unreliable, it is not included in the public-use dataset.

PHENOMS Microbiology Results v1

▼ CRF Header Info

Click the flag icon next to an input to enter/view discrepancy notes. Please note that you can only save the notes if CRF data entry has already started.

Exit

Microbi... (V6)

Title: Microbiology Results

Instructions: Enter all microbiology results obtained from Day 0 through Day 28 or ICU discharge, whichever occurs first. In addition, microbiology results prior to Day 0 (date of onset of sepsis induced organ failure) should be included if relevant to the current episode of infection.

Study day definitions

Study Day 0 (zero): Date of onset of sepsis induced organ failure 0000 to 2359
All other study days: 0000 to 2359
Discharge prior to day 28: 0000 to ICU discharge

Table name: Microbiology_Microbiology

| Date Specimen Collected (DD-MMM-YYYY) | Time Specimen Collected (HHMM) | Sample Site | Test Type | Test Result | If test result is positive or contaminant upload test report (including sensitivities) |
|---------------------------------------|-----------------------------------|--|--|--|--|
| <input type="text"/> MicroDay, # | <input type="text"/> MicroTime,\$ | <input type="text"/> SampleSite, # <small>(select one)</small> Site 1=Abscess 2=Blood 3=Bronchial brush 4=Bronchoalveolar lavage 5=Nasopharyngeal 6=Pleural fluid 7=Peritoneal fluid 8=Skin 9=Spinal fluid 10=Sputum 11=Stool / Rectal 12=Surgical site 13=Urine 14=Vascular catheter 15=Wound (non-surgical) 90=Other | <input type="text"/> TestType, # <small>(select one)</small> Type 1=Liquor 2=PCR 90=Other | <input type="text"/> TestResult, # <small>(select one)</small> Result 1=Positive 0=Negative 2=Contaminant | <input type="text"/> Click to upload file |

Add

Figure 1: Example of annotated case report form (CRF).

A.2 Accessibility of the Database

The CC of the AsA-NHPI Cohort Study is fully committed to making its data available for public use for interested investigators. We maintain the websites for our funded networks (including NIH-funded networks), and

we have traditionally maintained a study's data on the network's website. An illustrative example of our process to operationalize this is described. The websites for our two largest networks (CPCCRN and PECARN) allow users to navigate to a specific study conducted in the network. There, a user can obtain the protocol and the data forms, and previously, the user requested the data from the Utah DCC after obtaining IRB approval at the user's institution. In addition to our ability to make data available on the network website, we have extensive experience depositing public-use datasets into various NIH repositories. We anticipate deposit of the AsA-NHPI Cohort Study database, annotated CRFs, data dictionary, and details regarding the biospecimens stored in the biorepository for wide sharing via the NHLBI BioData Catalyst, and/or BioLINCC, and/or other NIH repositories as requested by NHLBI. Access to these databases is managed by NHLBI, assuring that the resources will be available even if the network is discontinued in the future.

A.3 Costs of Data

The cost of preparing the AsA-NHPI Cohort Study datasets for deposit onto NIH data repositories is assumed by the CC, and investigators will not be charged by the CC. The work is reflected by the personnel cost in our budget. There may be costs for investigators associated with obtaining datasets from BioLINCC in accordance with NIH policies and procedures which we do not account for.

B Biological Specimens Sharing Plan

B.1 Description of the Resource

This cohort study will collect biospecimens which will be stored at the Utah biorepository. We anticipate future ancillary projects will be written to analyze these biospecimens. The Ancillary Science Committee will be responsible for determining what samples are available for analysis based on reports provided by the CC. At the completion of the study, the CC will ship all biospecimens to a central biorepository as determined by NHLBI, along with data from OpenSpecimen as needed to continue to track the biospecimens. OpenSpecimen is fully described in the *Biospecimen Plan*.

B.2 Informed Consent for Specimen Usage

Informed consent documents used for the proposed study will include explicit language informing the participant that residual biological specimens, including DNA, may be stored in a biorepository for other scientific investigations. We anticipate using a layered consent procedure, which is described in the *Protection of Human Subjects* section of this proposal. This consent process was specifically recommended by community members during Needs Assessment performed in our preparation of this proposal.

B.3 Policies and Timing

These specimens will be used for peer-reviewed analyses, funded by additional NIH or other funding opportunities that are deemed acceptable to NIH by AsA-NHPI Cohort Study internal and external investigators. As mentioned above, the Ancillary Science Committee is responsible for determining which proposals are eligible to be evaluated by the network. The process for this is fully described in Section B.1.7 in *Overall Structure of the Study Team*.

When funded ancillary studies are completed, the Utah Biorepository will work with NHLBI to transfer specimens to NHLBI for biospecimens specifically collected for the ancillary studies and determine optimal methods for making the remaining samples available to other investigators. Policies for access and distribution to qualified investigators will be determined according to the policies of NHLBI.

C Genomic Data Sharing Plan

The Utah DCC and MPIs agree to abide by the NIH Genomic Data Sharing Policy for any genomic data generated from the AsA-NHPI Cohort Study, or future ancillary studies. We will comply with data submission expectations

and timelines, study registration in dbGaP, data deposit into the relevant NIH-designated repository, and informed consent requirements.

Protection of Human Subjects

This proposal includes key considerations for the AsA-NHPI Cohort Study protocol, modeled after other NHLBI cohort studies, and presents a starting point for the Steering Committee to consider. As such, we have included *Protection of Human Subjects* here.

A Risks to Human Participants

A.1 Human Participants Involvement and Characteristics

A.1.1 Overall Study Design

This cohort study will collect longitudinal clinical data and biospecimens from participants who self-identify as Asian American, Native Hawaiian, or Pacific Islander. The Schedule of Events and full study design will be developed during the UG3 phase of the project.

A.1.2 Participant Population to be Studied

Participants aged 25-64 who self-identify as Asian American, Native Hawaiian, or Pacific Islander will be eligible to enroll. A detailed list of inclusion/exclusion criteria will be developed during the finalization of the protocol in the UG3 phase.

A.1.3 Collaborating Sites Performing the Research

The sites that participate in this cohort study will be selected through a separate funding mechanism. It is anticipated there will be one Coordinating Center and 4-6 Clinical/Community Field Centers (CCFC). The CC will not enroll participants.

A.2 Study Procedures, Materials and Potential Risks

A.2.1 Study Procedures

Participants will have clinical data, clinical assessments, patient-reported outcomes, biospecimens, and other data collected at baseline and longitudinally. We propose follow-up visits every 6 months. We propose additional collection of biospecimens at year 2.

A.2.2 Study Materials

Appropriate study materials (e.g., protocol, consent forms) will be reviewed by the single IRB (SIRB) prior to implementation. Study specific SOPs, manuals, databases, statistical analysis plans, and other documents will be developed during the UG3 Phase.

A.2.3 Potential Risks

No intervention is planned. Potential risks of this observational cohort study include

- phlebotomy risks
- loss of confidentiality, including among members of the same household, as well as genomic data
- exacerbation of mental health conditions, triggered by assessment
- identification of a previously unknown disease

B Adequacy of Protection Against Risks

B.1 Informed Consent

All participants will provide informed consent prior to being enrolled in the AsA-NHPI Cohort Study using a SIRB-approved document.

Separate permission will be obtained from the participant to collect specimens that are to be used for DNA and RNA extraction and storage for future genetic analyses. Participation in the study will not be dependent on permission for genomic storage and analyses.

Genetic analysis would involve, in part, the analysis of genomic DNA and would attempt to link genotypic information to the extensive phenotypic information measured as part of this study. A layered informed consent will be used to obtain the participant permission for genetic testing. One potential approach would be to indicate individually:

- Permission for the AsA-NHPI Cohort Study
- Permission for collection of specimens for genomic data in the cohort study
- Permission for both of these categories.

There may be future analyses performed on data collected in this study. Those ancillary studies will be evaluated in their own right for the adequacy of their protection against risks, given the data and genomic material they intend to analyze.

The level of consent will be recorded in the database and retained at the clinical site. The level of consent will be stored in conjunction with the samples in the biorepository to maintain restrictions placed on usage during the consent process. OpenSpecimen, the tool we will use to maintain the biorepository (fully described in *Biospecimen Plan*) can track the level of consent associated with the biospecimen collected.

Upon completion and final closure of the AsA-NHPI Cohort Study, the CC will assign new study numbers for all study participants. The CC will then instruct the biorepository to strip all samples of their original study identifiers and re-label them with the new study numbers. This will prevent investigators from using the original study identifiers to identify individual participants in the future. These de-identified linked data and specimens will be submitted to NIH repositories.

Should participants revoke their permission for genetic testing prior to de-identification of specimens, the clinical site will notify the CC. The CC will then contact the biorepository and request that all samples collected for genetic analysis for that participant (identified by the original study number) be destroyed. Confirmation of destruction of samples will be sent to the CC and forwarded to the clinical site. Destruction of samples is only possible prior to final closure of the study; after that, there will be no way to identify samples since they will have been anonymized.

B.2 Institutional Review Board and Human Research Protection

The Institutional Review Board (IRB) at the University of Utah will serve as the SIRB. The Utah IRB has extensive experience with SIRB implementation as described in *Facilities and Other Resources*. No human participant research activities will be conducted at any 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 CCFC.

B.3 Protections Against Risk

B.3.1 Phlebotomy Risks

We anticipate blood will be collected regularly throughout the cohort study which has potential for phlebotomy risks. We will ensure the collection of appropriate volumes of blood samples recognizing participants may be

co-enrolled in other studies. Participants will be advised that phlebotomy may cause pain or bruising.

B.3.2 Loss of Confidentiality

The minimal risk of loss of confidentiality is mitigated by the substantial data management resources and security described in the *Facilities and Other Resources* section of this application. Genomic data are not generated during this cohort study, but rather the material to extract genomic data are stored. As such, there is no risk of the loss of confidentiality of genomic data from this study. Future ancillary studies may propose genomic analyses. Those studies will be evaluated for their risk of loss of confidentiality of genomic data.

B.3.3 Exacerbation of Mental Health Conditions by Assessment

We anticipate collecting a series of instruments related to mental health symptoms, which may identify participants with previously undiagnosed mental health conditions. Since lack of appropriate treatment may worsen these disorders, we anticipate the protocol will include procedures, developed in collaboration with the Community Advisory Board (CAB), for the local PI at the CCFC to address any findings, and refer the participant for evaluation and treatment.

B.3.4 Identification of a Previously Unknown Disease

We anticipate collecting biometric and lab data which may identify conditions or diseases which were previously unknown to the participant. This may cause distress to the participant. We anticipate the protocol will include procedures, developed in collaboration with the CAB, for the local PI at the CCFC to address any findings, and refer the participant for evaluation and treatment.

B.4 Vulnerable Populations

This cohort study is enrolling adult participants aged 25-64. There are no **children** included. As this is a study largely of cardiovascular, lung, and mental health conditions which affect adults, there is valid scientific rationale to exclude children from the longitudinal follow-up. Additionally, since the cardiovascular, lung, and mental health conditions which affect adults may be too advanced in geriatric populations, there is a valid scientific rationale to exclude older adults from the cohort study. We do not anticipate enrolling **prisoners**.

It is anticipated that pregnant women may be included. 45 CFR §46.204 describes additional protections for research involving **pregnant women and fetuses**. This study meets all of the conditions described for the inclusion of pregnant women in research as enumerated in 45 CFR §46.204, namely:

- a) there are no interventional drugs or devices which may generate potential risks to pregnant women or fetuses,
- b) the risk to the fetus is maternal phlebotomy, which is minimal risk,
- c) any risk is the least possible for achieving the objectives of the cohort study,
- d) there is no prospect of direct benefit to the pregnant woman or the fetus, and the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, and the maternal consent is obtained in accord with the informed consent provisions of 45 CFR §46,
- e) there is no prospect of direct benefit solely to the fetus, therefore paternal consent is not required,
- f) the informed consent document will describe reasonably foreseeable impact of the research on the fetus or neonate,
- g) no children are included in this study, therefore no children as defined in §46.402(a) who are pregnant are included,
- h) no inducements, monetary or otherwise, will be offered to terminate a pregnancy,
- i) individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy, and
- j) individuals engaged in the research will have no part in determining the viability of a neonate.

It is anticipated that persons with diminished or **questionable capacity to consent** may be included. These participants likely have cognitive disorders, or are those who develop cognitive disorders over the follow-up period

of the AsA-NHPI Cohort Study. The PI of the CCFC will evaluate potential participants for decisional capacity to consent to participate. It is anticipated that the Steering Committee will include tools and assessments to evaluate decisional capacity to consent as needed. The PI will then seek permission for enrollment from a legally authorized representative (LAR). Since the cohort study will offer no direct benefit to the participant, it is acceptable for the participant to decline enrollment, even if the LAR agrees to it.

Participants may also develop questionable capacity to consent over the follow-up period. In this circumstance, the PI of the CCFC will assess decisional capacity, and may need to seek consent for ongoing participation from an LAR. Since ongoing participation in the cohort study will offer no direct benefit to the participant, they may withdraw from the cohort study even if the LAR authorizes continued participation.

Because decisional capacity is study- and situation-specific, a participant may have capacity to consent for this low-risk cohort study protocol in usual circumstances, but that same participant may lack capacity to consent to higher-risk protocols or when under duress. This protocol is not high-risk, but it is anticipated that future ancillary studies may be proposed which are higher risk. Those proposals will be separately evaluated for their ascertainment of decisional capacity to consent in relation to the participant's duress and the risk of the proposed protocol.

C Potential Benefits of the Proposed Research

The potential benefit of the proposed AsA-NHPI Cohort Study is the development of generalizable knowledge about the prevalence of and risk factors for the cardiovascular, lung, and mental health conditions in Asian American, Native Hawaiian, and Pacific Islander populations. There is no direct benefit to the participant from participating in this research study.

D Importance of the Knowledge to be Gained

Knowledge gained from the AsA-NHPI Cohort Study will be critical to help quantify risk factors and incidences of cardiovascular, lung, and mental health conditions in the Asian American, Native Hawaiian, and Pacific Islander populations. Results from the study will help determine priorities and potential interventions to eliminate health disparities in these populations.

Delayed Onset Study Justification

The Utah CC will assist with development of the multi-center clinical protocol for the AsA-NHPI Cohort Study. We have included proposed entry criteria, visit schedules, questionnaires and instruments, and statistical considerations in *Research Strategy*. Additional details regarding proposed biospecimens to be collected are included in the *Biospecimen Plan*.

Progress Report Publication List

Not required/allowed since this is a new application, not a renewal.

Inclusion of Individuals Across the Lifespan

This cohort study is enrolling adult participants aged 25-64. There are no children included. As this is a study largely of cardiovascular, lung, and mental health conditions which affect adults, there is valid scientific rationale to exclude children from the longitudinal follow-up. Additionally, since the cardiovascular, lung, and mental health conditions which affect adults may be too advanced in geriatric populations, there is a valid scientific rationale to exclude older adults from the cohort study.

Vertebrate Animals

Not applicable.

Select Agent Research

Not applicable.

Consortium/Contractual Arrangements

The final Consortium will be developed after the CCFCs are selected. The Utah Data Coordinating Center (DCC) has extensive experience negotiating data-use agreements, sub-awards, and clinical trial agreements where the DCC has functioned as the coordinating center. We will utilize the same processes we have successfully used in all our prior networks to facilitate swift execution of contracts and sub-awards. Additionally, the Utah DCC manages several networks in which capitated payments are managed, tracked, and disbursed by the DCC.

Authentication of Key Biological and/or Chemical Resources

Not applicable.

Inclusion of Women and Minorities

This cohort study is enrolling adult participants aged 25-64 who self-identify as Asian American, Native Hawaiian, or Pacific Islander. There are no limitations on the participants' biologic sex or gender identity. This study is specifically targeted at traditionally underrepresented minorities in clinical research of the populations described. It is anticipated that persons who identify as multi-racial will be allowed to participate so long as they self-identify as Asian American, Native Hawaiian, or Pacific Islander.

Recruitment and Retention Plan

The Utah CC will not recruit participants for this cohort study. The Utah CC will coordinate CCFCs with their recruitment and retention efforts as described in *Research Strategy*. It is anticipated that the full Recruitment and Retention Plan will be developed in conjunction with the SC of the AsA-NHPI Cohort Study.

The Utah DCC has worked with enrolling sites in over 140 clinical research projects. We will draw upon the collective experience of Utah DCC staff, community advisors, investigators, study coordinators, and NIH staff to develop and implement a recruitment and retention plan.

Recruitment We anticipate participants will be identified using a variety of strategies including census tract data and CCFC knowledge of where the populations of interest tend to reside. Based on the community-based Needs Assessment that we conducted, enrollment in the community setting (churches, mosques, community health fairs, and other venues) was viewed more favorably than in the clinical setting. We recognize that other populations may favor a clinical setting so this option should still be available. Novel advertising approaches such as applications like TikTok and Nextdoor were recommended during the Needs Assessment as well. We anticipate using social media platforms like Facebook or Twitter and posting recruitment flyers at mosques, churches, restaurants, and other venues to advertise the study. We anticipate the CCFCs will cover the cost of advertising for recruitment and retention in their budgets, but the CC will assist in the creation of materials. Social media tools and other advertisements will have links to the website and a phone number to contact a member of the research team. CCFC staff and investigators will be encouraged to have a booth at community events where individuals can learn about the study. We are hopeful that participants will have a positive experience and refer other community members. Sharing study progress at community forums may also help recruitment.

Recruitment during the UG3 phase will be monitored by tracking weekly enrollment rates overall, by enrolling site, by participant sex, and by population of interest (Chinese and Tongan, for example). If concerns are raised in these domains, we will recommend the Recruitment and Retention Committee identify reasons and suggest solutions to the Steering Committee. We anticipate an iterative process during the UG3 phase and are capable of rapidly adapting so that an efficient recruitment process is implemented on schedule at the beginning of year 3 (beginning of UH3 phase).

The Utah DCC has been a Trial Innovation Center (TIC) since the inception of the Trial Innovation Network (TIN) in 2016. The TIN exists to support the design, conduct, analysis, and reporting of multi-center research projects in the National Center for Advancing Translation Science (NCATS) Clinical and Translational Science Award (CTSA) Network. One component of the TIN is the Recruitment Innovation Center (RIC). If funded, we will submit a TIN request for support for recruitment innovations from the RIC at the immediate outset of the protocol development phase for the AsA-NHPI Cohort Study. The RIC plans also include retention strategies.

Retention Retention strategies will be developed during the UG3 phase but will not be tested until the UH3 phase. Therefore, we are also anticipating an iterative process here as well. Trust is an important part of retention. We recognize that the study could be jeopardized if participants lose their trust in the scientific team or process. We take this very seriously and have already begun building relationships with community members. For instance, three members of the Utah DCC and MPI Raphael volunteered at the Utah Pacific Islander Health Coalition's MANA 5k walk on September 17, 2022. The Utah DCC intends to continue to attend local community events and present study progress and findings, approved by the Steering Committee and with community permission, at these events. CCFCs would be encouraged to share study progress at community forums as well. This practice will maintain engagement of enrolled participants and likely attract new participants. We believe retention will be enhanced if participants feel the study is contributing meaningful information. Based on the Needs Assessment we conducted, the participant newsletter and website were felt to be good ways to maintain interest in this way. Flexible scheduling and methods of data collection, for instance, collection of data online or in the home could facilitate efficient, informative study visits. Appropriate compensation for participant time and effort and conducting study visits in a culturally responsible manner are also important. Retention rates will be tracked and if concerns are noted, the Recruitment and Retention Committee will be tasked to identify potential reasons and suggest solutions to the Steering Committee.

Enrollment Reports Given the magnitude and scope of this project, it is essential that the CC provides CCFCs the resources necessary to recruit and retain participants. Enrollment reports that are easily accessible to the CCFCs are critical to this aspect of large multi-center research. In all of our studies, we create enrollment and follow-up reports. As shown as an example in Figure 1, a CCFC research coordinator can visualize the next expected visit and the corresponding date for the CCFC's enrolled participants. We summarize the protocolized window for the visit along with how long it has been since their most recent study visit. Coordinators access these reports daily to identify which participants require attention acutely and what evaluations might need to be performed. Enrollment reports summarizing overall study and site enrollment are created in a similar framework. Enrollment and retention summary reports are shown on every SC and Research Coordinator Committee meeting.

| Site | Subject ID | Baseline Visit Date | Next Expected Visit | Expected Date of Next Visit | Blood Draw visit | Target Window | | Visit Categorization Window | | Months from last CONQUER Visit | Most Recent Visit Date |
|-----------|------------|---------------------|---------------------|-----------------------------|------------------|---------------|-----------|-----------------------------|-----------|--------------------------------|------------------------|
| | | | | | | Begin Date | End Date | Begin Date | End Date | | |
| Site Name | 162-43 | 11/30/2021 | 6 months | 6/1/2022 | Yes | 4/1/2022 | 8/1/2022 | 3/1/2022 | 8/30/2022 | 8.8 | 11/30/2021 |
| | 162-22 | 12/10/2019 | 30 months | 6/10/2022 | No | 4/10/2022 | 8/10/2022 | 3/11/2022 | 9/8/2022 | 8.8 | 11/30/2021 |

Figure 1: Example Follow-up Report

In addition to having reports available to the network, our proposed CAB encompasses membership from community around the recruiting CCFCs. In the event that recruitment or retention lags expectations, we will enlist the assistance of the CAB to help sites determine alternative and novel ways to engage their participants.

Inclusion Enrollment Report

Not applicable. The AsA-NHPI Cohort Study has not begun.