National Institute of Neurological Disorders and Stroke

REPORT MONITORING ADHERENCE TO THE NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH AS REPORTED IN FY2022 – FY2024

National Institutes of Neurological Disorders and Stroke (NINDS)

Table of Contents

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I. Background/Overview

A. Mission statement

The National Institute of Neurological Disorders and Stroke (NINDS) mission is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease for all people. Included in this mission is the commitment to reducing the disproportionate burden of neurological disease borne by underserved groups of society, including racial and ethnic minoritized, rural, and socioeconomically disadvantaged populations, by funding a spectrum of research from basic science through clinical studies and training the next generation of health disparities investigators. NINDS also prioritizes research related to health conditions where women are either disproportionately affected or historically understudied.

The National Institutes of Health (NIH) has designated several U.S. populations as those that experience Health disparities (HDPs) and are in need of effective tailored prevention and treatment approaches (https://www.nimhd.nih.gov/about/overview/). Worse health outcomes in these populations when compared to the general US population have a dramatic impact on public health and are a significant cost to society. The NINDS supports research to diminish health disparities in neurological disorders, and it is inherent in the NINDS mission to reduce the burden of neurological disease, a burden borne by every segment of society. Through its mission, the NINDS strives to achieve the highest level of health for all people.

Description of NINDS portfolio

NINDS places a high priority on understanding and addressing disparities in the broad spectrum of neurological disorders across all HDPs. The largest part of the NINDS disparities portfolio addresses stroke and cerebrovascular disease, including vascular contributions to cognitive impairment and dementia (VCID), for which substantial disparities in incidence, mortality, and functional outcomes have been identified, and for which barriers to proven treatments and preventive approaches may exacerbate those disparities. Most disorders of the nervous system affect men and women with similar health impacts and in similar numbers, but some neurological conditions disproportionately affect women (e.g., migraine, chronic pain, multiple sclerosis, myalgic encephalopathy/chronic fatigue syndrome (ME/CFS), post-acute sequelae of COVD-19, stroke, and dementia) or have specific health implications for women (e.g., epilepsy and stroke risk during and after pregnancy, recovery after spinal cord and brain injury, and autism which affects males and females differently).

NINDS supports several epidemiologic and genetic studies, clinical trials, and disease specific clinical networks. Through these various research programs, the distribution, risk factors, determinants, and interventions for various neurological diseases are studied. Additionally, NINDS leads or co-leads several large-scale trans-NIH initiatives with Congressionally directed funded. Some of these initiatives include the Brain Research through Advancing Innovative Neuro-technologies (BRAIN) Initiative®, the Helping to End Addiction Long-term (HEAL) Initiative, Alzheimer's Disease and Alzheimer's Disease Related Dementias (AD/ADRD) research, and Researching COVID to Enhance Recovery (RECOVER), which includes examining disparate neurologic impact of the COVID-19 pandemic and long-term

sequalae of SARS COVID-19 (PASC) infection. In addition to these Congressionally directed programs, the NINDS continues to address unanticipated public health challenges and scientific opportunities in the prevention and treatment of neurological disorders through engagement with research partners across the NIH and beyond.

1. New NINDS-Led Initiatives

A. NINDS Community-Engaged Health Equity Research in Neuroscience Initiative (HERN)

In 2023, the NINDS launched the HERN initiative in direct response to the strategic goals outlined in the NINDS Health Equity Strategic Plan, which seeks to address and mitigate the disproportionate burden of neurological disorders in HDPs. These disparities often manifest as increased disease risk, poorer health outcomes, lower access to care, and greater vulnerability to conditions like stroke, Alzheimer's disease, and Parkinson's disease, among others.

The HERN Initiative represents a comprehensive, multi-pronged approach aimed at addressing health disparities in neurological diseases through community-engaged research and collaborative partnerships. The initiative has two primary goals:

1. Advancing health equity research across all neurological disease areas, with a specific focus on HDPs.
2. Supporting the development of collaborations, education, and capacity building to ensure that health equity research is not only conducted but sustained. This involves fostering partnerships between academic researchers, healthcare systems, community organizations, and policymakers to create a more inclusive and equitable research ecosystem.

In FY24, the first HERN R01 grant was awarded for the project titled “Advancing Community Connections and Calculating Risk to Optimize Stroke Survivorship (ACROSS)”. This project is designed to address the unique challenges faced by Black, Hispanic/Latino, and low-income populations, who experience a significantly higher risk and burden of stroke. Through the development of a simple, personalized intervention, ACROSS aims to bridge the gap between community resources and the healthcare system, providing tailored support to improve post-stroke outcomes. By engaging both healthcare professionals and community stakeholders, this project seeks to optimize stroke recovery and reduce disparities in post-stroke care for these underserved populations.

In addition to the ACROSS initiative, the HERN program is expected to fund additional grants in FY25 that will continue to focus on innovative, community-centered approaches to neurological health disparities. These efforts will explore a variety of neurological conditions and their disparate impacts on HDPs, while at the same time strengthening the infrastructure necessary to sustain equitable research.

B. Clinical Trial Readiness to Understand and Develop Solutions to Social, Ethical, Behavioral Implications and Barriers to Health Equity in ADRD

The Social, Ethical, Behavioral Implications and Barriers to Health Equity in ADRD (SEBI-ADRD) initiative seeks to establish clinical trial readiness for community-driven interventions to understand and develop solutions addressing barriers to equity in ADRD outcomes among HDPs. An R01 Research Project Grant notice of funding opportunity (RFA-NS-25-013) was published from Jun. 2024-Oct. 2024.

C. Native Collective Research Effort to Enhance Wellness (N CREW) Program

Led by the National Institute on Drug Abuse (NIDA), NINDS, and National Center for Advancing Translational Sciences (NCATS), N CREW aims to support Native American communities to conduct locally prioritized research to address overdose, substance use, and pain, including related factors such as mental health and wellness. N CREW aims to enhance research capacity by providing training, resources, and tools for research led by Tribes and Native American Serving Organizations. Research led by Native communities is essential for enhancing culturally grounded, strengths-based, effective, and sustainable intervention strategies.

D. Women's Health Research

Women's health research needs and opportunities are spread broadly across the neurological diseases and disorders within NINDS's mission space. NINDS established the Women's Health Interest Group (WHIG) in 2024 to better plan and coordinate efforts in women's neurological health. The WHIG provides resources, education, and a collaboration space for addressing NINDS interests in women's health. In addition to raising awareness and information sharing, goals of these meetings include brainstorming new efforts (e.g., funding opportunities, workshops, resources) to advance the understanding of neurologic diseases that may disproportionately or differentially affect women as well as improving the understanding of sex as a biological variable when conducting neurological research.

2. Extramural Epidemiological Studies (Select)

A. Reasons for Geographic and Racial Differences in Stroke (REGARDS)/VCID in a Bi-Racial Cohort

Launched in 2003, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) longitudinal national cohort study follows more than 30,000 participants to identify risk factors and social determinants of racial, geographic, and sex differences in stroke mortality and cognitive decline/dementia in the United States. The largest cohort of its kind, REGARDS has produced more than 650 research publications and contributed to more than 200 ancillary studies. For example, REGARDS studies have established the increased prevalence of several vascular risk factors in Black vs. White Americans. REGARDS investigators have also evaluated the harmful effects of diets high in added fats, fried food, eggs, processed meat, and sugary beverages and provided evidence that Mediterranean-style diets (i.e., high consumption of

plant-based foods and low intake of saturated fats) may be protective for stroke and cognitive impairment. For example, in a 2024 study (PMID: 39292985), REGARDS researchers found that, in middle-aged and older US adults who were cognitively intact at baseline, adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet was a better predictor of cognitive trajectory in Black participants than in White participants. Additionally, the MIND diet was associated with decreased risk of cognitive impairment in female participants but not male participants, with no difference between Black participants and White participants.

B. The Brain Attack Surveillance in Corpus Christi (BASIC) Study

The BASIC study is an over twenty-five year-long longitudinal, population-based, epidemiological study focused on Mexican Americans. This study has assembled a cohort of over 11,000 persons to examine the social determinants of stroke and stroke outcomes in this population. In the 2024 funding cycle, the BASIC study investigators will continue to monitor trends and ethnic disparities in stroke incidence, recurrence, 90-day outcomes and all-cause mortality. Because of previous work suggesting a rising stroke incidence in those 45-59 years of age, for the first time, BASIC will expand stroke surveillance and outcome assessments to include those 35-44 years of age, where preliminary data suggests that there is considerable stroke burden. Novel and innovative for this cycle of BASIC is a new mixed methods focus on risk and resilience mechanisms among Mexican American stroke survivors to determine factors that lead to better stroke outcome.

3. Extramural Clinical Networks and Studies (Select)

A. Stroke Network (NIH StrokeNet)

The NINDS established the NIH StrokeNet in 2013 to conduct phase 2 and phase 3 clinical trials and research studies to advance new approaches and treatments for acute stroke, stroke prevention, and recovery and rehabilitation following a stroke. The network includes central clinical and data coordinating centers and 27 regional recruitment coordinating centers that include over 550 stroke hospitals across the U.S. NIH StrokeNet serves as the primary infrastructure and pipeline for testing new potential treatments for patients with stroke and those at risk for stroke for studies funded by NINDS. StrokeNet has created an enrollment committee to assist in the development of strategies to engage women and HDPs. Examples of NIH StrokeNet trials, including their enrollment targets, are as follows:

i. Atrial Cardiopathy and Antithrombotic Drugs in Prevention after Cryptogenic Stroke Trial (ARCADIA)

In one-third of ischemic strokes, a specific cause cannot be identified. Recent evidence suggests that some cryptogenic strokes arise from left atrial thromboembolism that goes unrecognized because it is not associated with atrial fibrillation/flutter (AF) and patients do not receive anticoagulant therapy to prevent atrial thromboembolism. The ARCADIA trial is a multi-center, randomized controlled trial that will determine whether apixaban when given to patients with atrial cardiopathy, a biomarker that may indicate the source of the

clot was from the left atrium, is effective in preventing a second stroke. The trial completed enrollment in December 2022 enrolling 1015 participants into the trial and completed follow-up in February 2023. The primary results of the study were published in JAMA. 2024;331(7):573-581. Enrollment of minority participants exceeded pre-specified targets including 54% women, 8% Hispanics, 21% Black or African American, and 2% Asian.

ii. Multi-Arm Optimization of Stroke Thrombolysis Trial (MOST)

In the nearly 20 years since it was approved, intravenous tissue plasminogen activator (IV t-PA) remains the only approved pharmacologic therapy for the treatment of an acute ischemic stroke (AIS) and is estimated to improve neurologic outcome in ~30% of treated patients. Despite this benefit, it is estimated that IV t-PA only opens ~50% of occluded arteries one hour after treatment, reocclusion occurs in 14-34% of treated patients within 2 hours, and more than half of all IV t-PA treated patients are still disabled after 3 months. The addition of endovascular thrombectomy (ET) post IV tPA is a recent advance in the standard management of patients with large artery occlusion for whom tPA is not effective. Recent data from AHA/ASA Get with the Guidelines indicate that 93% of the acute care hospitals in the U.S. do not offer ET therapy and less than 9% of patients who get tPA will also get ET therapy. Thus, there remains an unmet clinical need for easily administered intravenous medications readily administered in any hospital that could improve the benefit of t-PA. The MOST trial is a three-arm, adaptive Phase 3 clinical trial that uses a Prospective, Randomized, Open treatment, and Blinded Endpoint (PROBE) design that compares two promising add-on drugs, Eptifibatide and Argatroban. The hypothesis was that when combined with t-PA either of these drugs could further reduce disability following an acute ischemic stroke. This study was a successful model of enrolling patient populations at risk for the disease. The study completed its enrollment in July 2023 with a total of 514 participants randomized. Enrollment minority participants met pre-specified targets including 48% of whom were women, 6% Hispanic, and 24% that were black or African American. The primary study results were published in The New England Journal of Medicine on September 4, 2024 (2024;391:810-820).

iii. Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)

Extracranial internal carotid artery atherosclerotic occlusive disease is a common cause of preventable stroke. Four to eight percent of adults have asymptomatic carotid stenosis exceeding 50%. Carotid stenosis is often managed either by endarterectomy (surgical removal of the clot) or stenting (placing a mesh tube in the artery to improve blood flow). In two independent multicenter, randomized controlled trials, CREST 2 is designed to compare the effectiveness of intensive medical management alone to carotid revascularization plus intensive medical management for prevention of stroke and death in individuals with high - grade stenosis but no symptoms. One trial will randomize patients to endarterectomy vs medical management and the second trial will randomize patients to carotid stenting with embolic protection vs medical management. CREST-2 reached its target enrollment in July 2024 by enrolling 2,486 participants into the trial: 1,241 in the endarterectomy trial and 1245 into the carotid stenting trials. Enrollment achieved their

sex/minority targets of 37% for women and 9% for minorities. This study will complete their primary endpoint follow-up by August 2025 with expected results reported by February 2026.

B. Strategies to Innovate EmeRgENcy Clinical Trials Network (SIREN)

SIREN is a clinical trials network funded by NINDS and the National Heart Lung and Blood Institute (NHLBI). The goal of the SIREN Network is to improve the outcomes of patients with neurologic, cardiac, respiratory and hematologic emergencies by identifying effective treatments given in the earliest stages of care. The SIREN Network is composed of a Clinical Coordinating Center, a Data Coordinating Center and 14 SIREN Hubs. Selected examples of current SIREN trials include:

i. Hyberbaric Oxygen Brain Injury Treatment (HOBIT) Trial

There continues to be an overarching problem of high mortality and poor outcome for victims of severe traumatic brain injury (TBI). Preclinical and clinical investigations indicate that hyperbaric oxygen (HBO2) has a positive impact on reducing brain injury and improving outcomes in severe TBI. HOBIT is enrolling consecutive eligible patients with TBI in the racial, ethnic, and sex distributions in which they present to clinical centers. The clinical centers are geographically dispersed across the U.S. and serve women and HDPs. For non-English speaking communities, consent and enrollment is achieved by utilizing the appropriate translators and language-specific informed consent documents, as determined by their local IRB's. Race, ethnicity, and sex are tracked and monitored in the study database and in the study screening log, both of which are part of the online data and trial management system, to ensure that the distribution among enrolled participants is not skewed from the distribution among eligible participants. This allows the investigators to monitor for disparities which can then be investigated to determine if any intervention is necessary to prevent disproportionate enrollment. Pregnant women are excluded from this protocol because of potential risk to the fetus. As of November, there are eight sites which have enrolled 138 of 200 patients.

HOBIT Ancillary Trial – The Biomarkers in the Hyperbaric Oxygen Brain Injury Treatment Trial (BioHOBIT)

This is an observational trial that is 1) validating the accuracy of candidate monitoring biomarkers for predicting clinical outcome; 2) determining the treatment effect of different doses of HBOT on candidate monitoring biomarkers; and 3) determining whether there is a biomarker defined subset of severe TBI that responds favorably to HBOT. This study will: 1) inform a go/no-go decision for a phase III trial of HBOT by providing adjunctive evidence of the effect of HBOT on key biological pathways through which HBOT is hypothesized to affect outcome; 2) provide evidence to support further study of the first monitoring biomarkers of severe TBI; 3) increase the likelihood of success of a phase III trial by identifying the sub-population of severe TBI likely to benefit from HBOT; and 4) create a repository of TBI biospecimen which may be accessed by other investigators. As of November 2024, 69

patients are enrolled.

ii. Brain Oxygen Optimization in Severe Traumatic Brain Injury – Phase 3 (BOOST-3)

TBI is a major cause of death and disability. Of the 3.5 million Americans who sustain a TBI every year, approximately 27,000 experience prolonged traumatic coma, the most severe form of TBI. Less than 20% of these patients make a good recovery, and most are left with life-long disabilities. ICU management of severe TBI focuses on monitoring intracranial pressure (ICP), but data from recently conducted randomized clinical trials indicate that this approach is overly simplistic. Clinical studies demonstrate that brain tissue hypoxia is common, that there is a strong relationship between low partial pressure of oxygen in brain tissue (PbtO2) and poor outcome, and that timely interventions can reverse brain tissue hypoxia. BOOST-3 trial will determine if there is evidence of clinical efficacy of a treatment protocol based on PbtO2 monitoring compared to treatment based on ICP monitoring alone. Women will be included in this trial and sex will not be a selection criterion. It is anticipated that approximately 70% of the participants will be male, reflecting the demographics of TBI. Minorities will also be included in this study, and race/ethnicity will not be a selection criterion. It is anticipated that the race/ethnic distribution of participants in this trial will be similar to the communities served by the trauma centers participating in the study. The SIREN network and NETT, its predecessor, have been successful in enrolling participants belonging to ethnic and racial minorities, in a distribution similar to that seen in the local Trauma Registries. As of November 2024, 45 sites have enrolled 709/1094 patients.

iii. Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients (ICECAP)

Neurological death and disability are common outcomes in survivors of cardiac arrest. Therapeutic cooling of comatose patients resuscitated from shockable rhythms markedly increases the rate of good neurological outcomes, but poor outcomes still occur in as many as 50%, and the benefit of cooling in those resuscitated from asystole and pulseless electrical activity has not been shown in a randomized study. The ICECAP study is enrolling comatose adult survivors of out-of-hospital cardiac arrest that have already been rapidly cooled using a definitive temperature control method. Women are included in this study, and sex will not be a selection criterion. It is anticipated that approximately 65% of participants will be male, reflecting the demographics of victims of out-of-hospital cardiac arrest. Minority groups will be included in the study, and race/ethnicity will not be selection criteria. The study investigators anticipate that the race/ethnic distribution of subjects in the study will be similar to the communities served by participating hospitals and will be similar to the ethnic distribution of patients enrolled in trials of out-of-hospital cardiac arrest performed by the Resuscitation Outcomes Consortium, which included many of these same or similar sites. SIREN also includes many sites from the NETT Network, which has been successful in enrolling ethnic minorities in clinical trials in representative distributions. As of November 2024, 45 sites have enrolled 1030/1800 patients.

ICECAP Ancillary Trial - Precision Care in Cardiac Arrest: Influence of Cooling duration on

Efficacy in Cardiac Arrest Patients (PRECICECAP)

This study is applying machine learning to high-resolution, multimodality data collected from patients resuscitated from out-of-hospital cardiac arrest. The aim is to discover novel biomarker signatures to predict the optimal duration of therapeutic hypothermia and 90-day functional outcomes. In parallel, the team are developing a freely available software platform for standardized curation of intensive care unit-acquired data for machine learning applications. As of November 2024, 45 sites have enrolled 138 patients.

iv. Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients (P-ICECAP)

This is a multicenter trial to establish the efficacy of cooling and the optimal duration of induced hypothermia for neuroprotection in pediatric comatose survivors of cardiac arrest. As of November 2024, 47 sites enrolled 227/900 patients.

C. Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT)

The Network for Excellence in Neuroscience Clinical Trials, or NeuroNEXT, was created to conduct studies of treatments for neurological diseases through partnerships with academia, private foundations, and industry. NeuroNEXT has created a Recruitment Committee to assist in the development of strategies to address recruitment needs. This committee proactively works with study teams to develop and review plans to allow for maximum study accrual and retention. Committee members have also led educational presentations on recruitment strategies, data collection, reporting, and methods to enhance the appropriate representation of patient populations in the trials. The committees have created a variety of tools that can be utilized in any study. Examples include: Specific talking points during approach to potential participants; frequently asked questions page, brochures, newsletters, fliers, and website postings for local use; participant videos including study specific videos or disease specific videos; “Dear Doctor” letters for specialist physician referrals outside of the study site; recruitment grid templates for sites with competing trials; appropriate use of social media outlets, general recognition for time and participation; participant webinars and teleconferences; and attendance of disease-specific support groups and patient advocacy meetings by specialty groups or foundations.

A Phase-2b, Double-Blind, Randomized Controlled Trial to Evaluate the Activity and Safety of Inebilizumab in Anti-N-methyl-D-aspartate receptor (NMDAR) Encephalitis and Assess Markers of Disease

N-methyl-D-aspartate receptor (NMDAR) encephalitis is one of the most common causes of autoimmune encephalitis, with prevalence exceeding herpes encephalitis in industrialized nations. Typically, the disease affects patients ages 10-50 causing prominent psychiatric symptoms, associated with declining consciousness, seizures, movement disorders and life-threatening dysautonomia. Intensive care, including cardiorespiratory support is required in 75% of cases. Inebilizumab is a promising therapeutic monoclonal antibody for the treatment of NMDAR encephalitis. Compared to other off label B-cell depleting therapies, such as rituximab, inebilizumab not only depletes CD20+ B-cells, but also CD20- plasma blasts and plasma cells, resulting in robust,

broad and sustained suppression of B-cell expression. The Extinguish Trial will randomize 116 participants with moderate-to-severe NMDAR encephalitis to receive either inebilizumab or placebo in addition to first-line therapies. The results of the Extinguish Trial may immediately impact patient care and will facilitate the design and implementation of future clinical trials in patients with autoimmune encephalitis. To date, 43 participants have been randomized: 77% female, 35% black or African American and 40% Hispanic/Latino.

D. Pediatric Studies (Select)

i. Mechanisms of Cerebral Infarcts and Brain Oxygen Utilization in Anemia

While cerebral oxygen delivery depends on the cerebral blood flow (CBF; ml blood/100g tissue/minute) and blood oxygen content, it is becoming increasingly recognized that blood capillary transit time itself can also influence tissue oxygen extraction, even in the presence of normal or elevated CBF. In individuals with anemia where accelerated capillary flow velocities may be present as a result of hyperemia and cerebral autoregulation, reduced capillary transit time can lead to reduced times for tissue oxygen offloading. Compelling evidence has been provided for heterogeneous capillary flow underlying abnormal oxygen delivery in multiple conditions including expansion of infarcts in acute ischemic stroke, traumatic brain injury, and Alzheimer's disease. In sickle cell anemia (SCA), the investigators observed that rapid capillary transit, visible on arterial spin labeling (ASL) CBF-weighted MRI, is present in more than 50% of adults and children. They showed in published work and preliminary data from 154 adults and children with SCA that hyperintense ASL signal within cerebral dural venous sinuses is directly associated with elevated arterial velocities, elevated CBF, and reduced oxygen extraction fraction (OEF; ratio of oxygen consumed to oxygen delivered), and that this effect may reduce following transfusion therapies that improve oxygen delivery to tissue.

These findings indicate that venous hyperintense signal on ASL images may represent a marker of capillary-level disturbances in oxygen exchange efficiency. They observed (in preliminary work) that rapid capillary-level arterio-venous transit is associated with reduced oxygen metabolism, suggesting that these transit times may provide a biomarker of cerebral ischemia in individuals with SCA who have greater than a 50% risk of cerebral infarcts by age 30 years, yet often lack conventional stroke risk factors. In this study, the investigators propose to refine neuroimaging methods for evaluating arterio-venous transit to allow for robust, quantitative measures of capillary transit time non-invasively in vivo, and subsequently to test fundamental hypotheses regarding cerebral oxygen utilization in anemic individuals with vs. without infarcts. Aim (1): To apply innovative ASL MRI methods and time regression analyses over major intracranial arteries and dural sinuses in healthy control and SCA participants. Aim (2): To quantify cerebral capillary transit time in SCA participants before and after treatment with blood transfusion to understand how increases in hemoglobin parallel an improvement in brain oxygen extraction. Aim (3): To test the hypothesis that arterio-venous transit times are reduced in individuals with SCA with versus without infarcts. The short-term goal is to utilize non-invasive imaging approaches to understand mechanisms of oxygen utilization and neurovascular dysfunction

in anemia. The long-term goal is to use this information to triage individuals with anemia for personalized stroke prevention therapies, as well as to objectively quantify the impact of these therapies on brain health. This study is in its third year. Enrollment to date is 50 participants (of 150 expected), with 47 Black/African American Non-Hispanic/Latino and 3 White (one of whom is Hispanic/Latino). 29 are female, 21 are male; 14 are in the 6–12-year-old age group, 9 are 18-25, and 21 are 26-45.

ii. FOCAS Trial: Focal Cerebral Arteriopathy (FCA) Steroids

Focal Cerebral Arteriopathy (FCA) is a condition that causes narrowing of the blood vessels in the brain and is a common cause of arterial ischemic stroke (AIS) in children. Although rare overall, FCA is one of the most common causes of arterial ischemic stroke in a previously healthy child and often progresses dramatically over days to weeks. A 2017 European retrospective cohort study suggested that corticosteroid treatment may improve outcomes for FCA (Steinlin M, Stroke 2017). To evaluate the comparative effectiveness of steroid treatment compared to standard care in US children in "real world" treatment settings, NINDS launched the Focal Cerebral Arteriopathy Steroids (FOCAS) Trial in 2024. Based on FCA enrollment figures from other cohorts, it is anticipated that approximately 54% of the subjects will be female, 64% will be Non-Hispanic White, 10% Asian, 6% Hispanic White, 5% Black/African American, 2% First Nation or Native American, and 13% will be mixed or unknown races.

E. Alzheimer's Disease and Alzheimer's Disease Related Dementias (AD/ADRD)

In 2017, NINDS launched the Consortium for Detecting Cognitive Impairment, Including Dementia (DetectCID), which is a multi-site study developing, testing, and validating several novel cognitive impairment assessments designed to be easy to perform in primary care setting, relatively quick, and not affected by reading level or ethnic/cultural differences among patients. DetectCID is now conducting Phase 2 clinical trials of the most promising assessments identified in the first phase (2017-2021) with a larger number of research participants – at least half of which are from racial/ethnic minority groups. In 2024, the first Phase 2 clinical trial results were published showing that, compared to standard care, a five-minute cognitive assessment (known as 5-Cog) coupled with a follow-up care decision tree significantly improved measures of dementia diagnosis and care among 1,200 predominantly Black and Hispanic American older adults (PMID: 38834847). For example, use of the 5-Cog tool improved the odds three-fold that a patient would receive dementia-related care compared to standard practice.

Between FY22-24, NINDS released four funding opportunities addressing health disparities research in AD/ADRD: PAR-22-221 (AD/ADRD, Adverse Childhood Experiences, and Social Determinants of Health Ancillary Studies of Existing Longitudinal Cohort); RFA-NS-23-001 (Pragmatic Clinical Trials in Community Settings to Decrease or Prevent VCID Outcomes, Including in Populations that Experience Health Disparities); RFA-NS-24-024 (Role of Environmental Stress in the Health Inequities of Alzheimer's Disease-Related Dementias (ADRD); and RFA-NS-25-013.

F. HEAL-EPPIC-NET

NINDS established the Early Phase Pain Investigation Clinical Network (EPPIC-Net) as a part of the NIH HEAL (Helping to End Addiction Long-term) Initiative. EPPIC-Net's mission is to accelerate and enhance clinical testing of novel, non-addictive pharmacologic and non-pharmacologic therapeutic "assets", including new and repurposed small molecules, biologics, natural products, and devices, targeted to pain conditions of high unmet need. EPPIC-Net has conducted cutting-edge Phase II clinical trials (CTs) across the age and pain condition spectrum of pain therapeutics submitted by industry, academic, and other partners and accepted after rigorous review. EPPIC-Net provides access to a robust CT network with expert infrastructure providing study design, conduct, and analysis at no cost to the applicant. The network consists of a Clinical Coordinating Center (CCC; MGH), a Data Coordinating Center (DCC; NYU), and 12 Specialized Clinical Centers located across the US.

The EPPIC-Net Program has become a successful NINDS/HEAL Phase II CT program that was created and managed by a small NINDS team, with the assistance of disease-specific experts within the network at the coordinating centers and is NINDS' first program to use OT funds. The CCC and DCC infrastructure and resources provided by the EPPIC-Net provides a unique centralized structure supporting asset-holder initiated applications for CTs for any pain condition where the current treatments are either opioid-based or lack effective treatments. To date, 95 applications were received at the preliminary stage, with 22 moving onto the second (dossier) stage. Seven applications were submitted at the protocol stage with three being approved for funding.

To date, the EPPIC-Net has provided full protocol development, biostatistical support, data and safety monitoring, clinical and data coordination, and recruitment and retention support for two ongoing CTs. EPPIC-Net completed data collection on its first Phase II CT, EN20-01, a 24-week study to evaluate the safety and efficacy of CNTX-6970 in subjects with moderate to severe knee osteoarthritis pain. This multi-period crossover randomized, controlled trial allows comparability and assessment of efficacy through repeated exposures within each subject to the active treatment and a control (placebo) in randomized sequence. Study site closeout is nearing completion and data analysis will commence shortly.

The other ongoing CT, EN21-01, is a multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of 80 mg daily of NRD135S.E1 versus placebo in adult and elderly participants with painful diabetic peripheral neuropathy (PDPN) (SERENDIPITY-1). The purpose of this study is to investigate the safety and efficacy of NRD135S.E1 80 mg once daily in the treatment of PDPN when administered for 13 weeks. As of August 2024, the study has randomized 70 participants (57% of the enrollment target); enrollment is expected to be complete by Summer 2025.

G. Parkinson's Disease

i. Study in Parkinson Disease of Exercise (SPARX3)

This study is a Phase 3 multi-site, randomized, evaluator-masked study of endurance

treadmill exercise on changes in the Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) Part III score at 12 months among persons with early-stage Parkinson disease. The study objective is to establish the efficacy of high-intensity endurance exercise as first-line therapy for early stage, levodopa naïve people with Parkinson's disease (PD). If successful, this study could have a significant impact on the quality of life of people with PD and their caregivers as well as public health since it may slow progression of the signs of PD. Establishing high-intensity endurance treadmill exercise as a means to slow the progression of the signs of the disease would mark a significant breakthrough in treating PD and would have a significant public health impact. The study population will consist of both men and women. Because Parkinson's disease is more prevalent among men than women, this trial plans to enroll 57% men and 43% women. The risk of developing PD is twice as high in men than women, but women have a higher mortality rate and faster progression of the disease. Moreover, motor and nonmotor symptoms, response to treatments, and disease risk factors differ between women and men. Each study site will implement extensive outreach programs to make sure that the study recruits its targeted enrollment sample. Additionally, target enrollment is 5% each for African American, Hispanic, Latino, and Asian participants. The study team is implementing multiple approaches that will be overseen by an expert who has developed a rigorous framework for recruiting racial and ethnic minorities to clinical trials conducted within specialty clinics.

H. Amyotrophic Lateral Sclerosis (ALS)

NINDS has made strides to implement the Accelerating Access to Critical Therapies for ALS Act (ACT for ALS; PL 117-79), which was signed into law in 2021 to support treatment advances in ALS. With direct Congressional appropriations, new ALS studies have been funded. For example, the Access for All in ALS (ALL ALS) Clinical Research Consortium is conducting a large natural history study of ALS biomarkers, symptomology, and outcomes. The ALL-ALS consortium consists of 35 clinical sites across the United States and Puerto Rico. To foster wide representation across populations, data is being collected from both remote and in-person visits to facilitate enrollment for individuals who may not live close to major ALS centers. A majority of clinical sites are located in geographical areas with high representation of women and HDPs, which should help the study investigators reach their enrollment goals. ALL ALS also plans to build a second language study website (in Spanish) to expand outreach.

I. Undiagnosed Diseases Network

The Undiagnosed Diseases Network (UDN) is a research program supported by NIH that combines basic and clinical research services to understand health conditions for individuals and their families who have sought a clinical diagnosis without success. Launched by the NIH Common Fund in 2013, the UDN has built an international reputation for advancing disease research while establishing exemplary clinical practices for undiagnosed diseases. Between 2013 and 2023, the UDN facilitated difficult diagnoses for almost 700 people – providing answers to patients who have long searched for the cause

of their symptoms. Through team science and collaboration, UDN investigators have discovered hundreds of novel disease-associated genes and genomic variants, including the identification of new diseases and syndromes. In 2023, the UDN transitioned from the Common Fund to an NIH-wide initiative, with support from 17 NIH Institutes and Centers (Phase III) under the leadership of NINDS. The current network consists of a Data Management and Coordinating Center (DMCC), which provides infrastructure and research support for 24 clinical sites. The DMCC also supports Research Cores for services such as genomic sequencing, functional studies in model organisms, and consultation for metabolomic and proteomic analysis, based on the needs of cases being assessed by the network.

The NINDS envisions the UDN evolving into a larger self-sustaining network that fosters scientific discovery and provides expert diagnostic services for undiagnosed patients across the nation. Priorities for the UDN in Phase III are to: 1) Scale clinical capacity to engage more patients by increasing the efficiency and cost-effectiveness of the diagnostic evaluation; 2) Expand access to the UDN for HDPs; 3) Continue to incorporate input from patients, caregivers, and family members into the practice of the UDN; 4) Continue fruitful genetic investigations, and expand to other potential causal factors such as environmental insults, infectious, oncologic, immunologic, or complex multi-organ disorders; 5) Continue to develop health economics approaches to support the sustainability of the UDN approach to investigate persons with undiagnosed medical conditions; and 6) Incorporate implementation science methods to facilitate the translation of lessons learned through the UDN into mainstream medical care.

4. Intramural Clinical Study (Select)

a. Immuno-Virological Evaluation of Human T Cell Lymphotropic Virus (HTLV) Infection and Associated Neurological Diseases

This is a longitudinal observational study of HTLV- related disease. Asymptomatic seropositive individuals, those with sero-indeterminate HTLV serology and healthy volunteers serve as control cohorts. Subjects are evaluated on an annual basis with imaging, laboratory and clinical evaluations. HTLV is a human retrovirus; most common infections are asymptomatic, however in less than 5% of infected individuals they are associated with a progressive myelopathy. HTLV infection is endemic in certain regions, including Japan, the Caribbean, and some areas of the Middle East. In the United States, infection is most commonly seen among people of African and Afro-Caribbean descent. This study is currently recruiting participants. Thus far, 474 participants have enrolled, including 62% women and 47% African American.

II. Strategies for Ensuring Compliance

A. Peer Review

The implementation of inclusion guidelines involves the participation of review, program, policy, and grants management staff. Following specific guidelines, reviewers on NIH peer review panels or Scientific Review Groups (SRGs) evaluate applications for the appropriateness of the proposed plans for inclusion of women, racial and ethnic minorities, and participants across the lifespan in applications proposing clinical research. For NIH-defined Phase 3 clinical trials, applications are further assessed for plans to conduct valid analyses of intervention effects among women and racial and ethnic groups. Unacceptable inclusion plans must be reflected in the priority score and documented in the summary statement of the application. SRGs make recommendations regarding the acceptability (scientific justification) of the proposed study population. If issues are raised during review, Program staff notify the applicants who are required to address these issues prior to funding. Applications with unacceptable inclusion plans receive a bar to funding; an award is not issued until an acceptable resolution is received. To resolve inclusion issues, an applicant must address the problems identified by SRG and submit revised inclusion plans to Program staff. After Program staff has approved the documentation, grants management staff are notified of the resolution and forwarded any supporting /resolution documentation which becomes a part of the applicant's grant folder. In addition, reporting of analyses by sex and race/ethnicity in Clinicaltrials.gov is required for all applicable clinical trials within 12 months of the primary completion date.

B. Program Monitoring and Grants Management Oversight

Prior to award, Program Officials/Directors review the application inclusion information to determine whether the proposal plans are scientifically appropriate for the NINDS mission. Applications are then assigned to the designated Program staff to provide consultation, monitor the trial milestones, enrollment progress, and annual progress reports. Research investigators are consulted if specific concerns need to be addressed. For NIH-defined Phase 3 clinical trials, Program Officials/Program Directors monitor the requirement for sex and race/ethnicity analyses in applications and annual progress reports. Grants management staff ensure that appropriate terms and conditions of award are included in the Notice of Award, and that this information is appropriately documented in the official grant file.

C. Intramural Research Program (IRP)

All intramural clinical research studies require investigators to provide plans for the appropriate inclusion of women and minorities and/or a justification whenever representation is limited or absent, as part of their NIH protocol reviews. A central intramural NIH Institutional Review Board (IRB) evaluates research protocols for compliance with inclusion guidelines and conducts annual monitoring. With each annual review and renewal, the investigator documents the number, sex and race and ethnicity of those who were accrued during the past year; any issues with accrual are addressed at the annual review by the investigator and reviewed by the IRB. Also, the Clinical Center's Office of Protocol Services (OPS) coordinates annual reporting of demographic participant data to the Office of Extramural Research (OER) and the Office of Research on Women's Health.

D. NINDS Training Approaches

NINDS Officials/Program Directors and Scientific Review Officers recently completed the NIH-wide online HSS and Other eRA Systems for Monitoring Human Subjects Research training modules. These modules were updated in 2020 and contain modules on inclusion. Staff may access these modules via NIH intranet at any time. Additionally, NINDS staff received training on clinical trial inclusion during annual NINDS New Hires training and Division of Clinical Research (DCR) led outreach training.
https://era.nih.gov/era-training/era-videos.htm?q=era_training/era_videos.cfm#HSCT-Overview .

In the Intramural Program, a "Clinical Trials Bootcamp" Interactive workshop for the NINDS Neurology Clinical Research Fellows took place on the NINDS intramural campus. The Bootcamp, intended to orient new NINDS clinical fellows to clinical trials methodology and regulatory science, included a session using a case study approach to highlight some of the key aspects of ethical enrollment in clinical research populations. Other methods to support clinical operations and monitoring of neurological diseases research is forthcoming.

E. Additional NINDS Tools and Practices used to Ensure Compliance with The Inclusion Policy

Sub-optimal clinical research recruitment and retention of under-represented and underserved populations are well-known health equity barriers. There is a paucity of best-practice guidelines for improving recruitment, engaging HDPs and reducing accrual barriers in these under- represented communities. The NINDS responses to these issues include providing investigator support through sharing successful engagement practices between trials, brainstorming sessions, and assisting with operational planning for the recruitment/retention of women and HDPs. In 2021, an NINDS workgroup was created to review and implement best practices.

NINDS provides support for Networks and individual trial efforts to identify and overcome enrollment barriers. NINDS Program staff work collaboratively with the study team to improve enrollment of women and racial and ethnic minorities.

Lastly, two of our clinical networks, NeuroNEXT and StrokeNet, have created enrollment committees to assist in the development of strategies to address women and HDPs. The committees proactively work with study teams to develop and review plans to allow for maximum study accrual and retention of people at risk for the neurological diseases being studied.

Committee members have also led educational presentations on recruitment strategies, data collection, reporting, and methods to enhance community engagement in trials. The committees have created a variety of tools that can be utilized in any study. Examples include: Specific talking points during approach to potential participants; frequently asked questions page, brochures, newsletters, fliers, and website postings for local use; participant videos including study specific videos or disease specific videos; Dear Doctor letters for specialist physician referrals outside of the study site; recruitment grid templates for sites with competing trials; appropriate use of social media outlets, general recognition for time and participation; participant webinars and teleconferences; and attendance of disease-specific support groups and patient advocacy

meetings by specialty groups or foundations.

F. Special Focus on Inclusion, Recruitment and Retention

The NINDS is committed to reducing the disproportionate burden of neurological disease borne by underserved groups of society, including racial and ethnic minority, rural, and socioeconomically disadvantaged populations, by funding a spectrum of research from basic science through clinical studies and training the next generation of health disparities investigators.

III. Analysis and Interpretation of Data

1. Appendix A: IC Aggregate Inclusion Data Tables, NIH-Defined Extramural and Intramural Clinical Research

Appendix A.1

Table 1. Total Inclusion Enrollment Records (IERs) for NIH-Defined Extramural and Intramural Clinical Research Reported Between FY2022 and FY2024

Fiscal Year	Total IERs	IERs Without Enrollment*	IERs With Enrollment	US Site IERs	Non-US Site IERs	Female Only IERs	Male Only IERs	IERs Excluding Male-only and Female-only**
2022	1,115	401	714	662	52	23	34	657
2023	1,100	362	738	677	61	28	31	679
2024	1,081	315	766	725	41	23	30	713

* IERs Without Enrollment – Reflects IERs/studies that have not yet enrolled participants
**Inclusion Data Records (IERs) excluding male-only and female-only include unknown sex, and combination of unknown and any sex.

Appendix A.2

Table 2. Enrollment for All NIH-Defined Clinical Research by Sex

Fiscal Year	Sex	Total Enrollment	Total (%)	Minority Enrollment*	Minority (%)
2022	Female	79,055	50.8	41,656	52.7
2022	Male	73,565	47.3	36,236	49.3
2022	Unknown	3,006	1.9	119	4.0
2023	Female	103,181	53.4	63,682	61.7
2023	Male	86,488	44.8	46,287	53.5
2023	Unknown**	3,460	1.8	163	4.7
2024	Female	73,324	50.2	29,584	40.3
2024	Male	69,002	47.2	24,538	35.6
2024	Unknown	3,789	2.6	215	5.7

*Minority enrollment includes participants within all racial categories except White and Unknown, and participants identified as Hispanic/Latino, regardless of race classification. Therefore, total minority enrollment cannot be deduced from aggregate race and ethnicity totals.
**Increase in Unknown in FY24 is due in part to the addition of IERs involving de-identified research samples and patient records lacking data on sex and race/ethnicity.

Appendix A.3

Table 3. Enrollment for All NIH-Defined Clinical Research by Sex and Race

Fiscal Year	Sex	American Indian / Alaska Native	American Indian / Alaska Native (%)	Asian	Asian (%)	Black/ African American	Black / African American (%)	Native Hawaiian / Pacific Islander	Native Hawaiian / Pacific Islander (%)
2022	Female	757	1.0	4,702	5.9	18,196	23.0	119	0.2
2022	Male	504	0.7	4,048	5.5	13,649	18.6	113	0.2
2022	Unknown	5	0.2	26	0.9	18	0.6	0	0.0
2023	Female	825	0.8	3,590	3.5	36,488	35.4	115	0.1
2023	Male	621	0.7	3,569	4.1	20,172	23.3	106	0.1
2023	Unknown	6	0.2	43	1.2	35	1.0	0	0.0
2024	Female	307	0.4	5,000	6.8	14,498	19.8	138	0.2
2024	Male	389	0.6	4,544	6.6	12,269	17.8	138	0.2
2024	Unknown	6	0.2	40	1.1	41	1.1	21	0.6

Appendix A.3.1

Table 3.1. Enrollment for All NIH-Defined Clinical Research by Sex and Race - continued

Fiscal Year	Sex	White	White (%)	More Than One Race	More Than One Race (%)	Unknown / Not Reported	Unknown / Not Reported (%)
2022	Female	46,806	59.2	1,532	1.9	6,943	8.8
2022	Male	47,199	64.2	1,297	1.8	6,755	9.2
2022	Unknown	99	3.3	8	0.3	2,850	94.8
2023	Female	54,275	52.6	1,365	1.3	6,523	6.3
2023	Male	54,201	62.7	1,076	1.2	6,743	7.8
2023	Unknown	416	12.0	19	0.5	2,941	85.0
2024	Female	45,737	62.4	1,725	2.4	5,919	8.1
2024	Male	44,360	64.3	1,256	1.8	6,046	8.8
2024	Unknown	302	8.0	56	1.5	3,323	87.7

Appendix A.4

Table 4. Enrollment for All NIH-Defined Clinical Research by Sex and Ethnicity

Fiscal Year	Sex	Not Hispanic	Not Hispanic (%)	Hispanic Latino	Hispanic Latino (%)	Unknown Not Reported	Unknown Not Reported (%)
2022	Female	57,298	72.5	17,709	22.4	4,048	5.1
2022	Male	51,292	69.7	17,932	24.4	4,341	5.9
2022	Unknown	190	6.3	63	2.1	2,753	91.6
2023	Female	76,702	74.3	22,704	22.0	3,775	3.7
2023	Male	59,987	69.4	22,203	25.7	4,298	5.0
2023	Unknown	624	18.0	64	1.8	2,772	80.1
2024	Female	58,481	79.8	9,387	12.8	5,456	7.4
2024	Male	55,636	80.6	7,397	10.7	5,969	8.7
2024	Unknown	466	12.3	83	2.2	3,240	85.5

2. Appendix B: IC Aggregate Inclusion Data Tables, NIH-Defined Extramural and Intramural Phase III Clinical Trials

Appendix B.1

Table 5. Enrollment for All NIH-Defined Extramural and Intramural Phase III Clinical Trials by Sex

Fiscal Year	Sex	Total Enrollment	Total (%)	Minority Enrollment	Minority (%)
2022	Female	2,553	39.7	442	17.3
2022	Male	3,861	60.0	674	17.5
2022	Unknown	17	0.3	0	0.0
2023	Female	2,355	38.4	422	17.9
2023	Male	3,762	61.3	490	13.0
2023	Unknown	23	0.4	0	0.0
2024	Female	8,845	45.5	3,627	41.0
2024	Male	10,592	54.4	3,735	35.3
2024	Unknown	19	0.1	2	10.5

Appendix B.2

Table 6. Enrollment for All NIH-Defined Extramural and Intramural Phase III Clinical Trials by Sex and Race

Fiscal Year	Sex	American Indian / Alaska Native	American Indian / Alaska Native (%)	Asian	Asian (%)	Black / African American	Black / African American (%)	Native Hawaiian / Pacific Islander	Native Hawaiian / Pacific Islander (%)
2022	Female	12	0.5	42	1.6	281	11.0	2	0.1
2022	Male	22	0.6	82	2.1	299	7.7	12	0.3
2022	Unknown	0	0.0	0	0.0	0	0.0	0	0.0
2023	Female	9	0.4	34	1.4	302	12.8	0	0.0
2023	Male	17	0.5	66	1.8	227	6.0	12	0.3
2023	Unknown	0	0.0	0	0.0	0	0.0	0	0.0
2024	Female	28	0.3	154	1.7	2,441	27.6	22	0.2
2024	Male	49	0.5	236	2.2	2,133	20.1	32	0.3
2024	Unknown	0	0.0	2	10.5	0	0.0	0	0.0

Appendix B.2.1

Table 6.1. Enrollment for All NIH-Defined Extramural and Intramural Phase III Clinical Trials by Sex and Race – continued

Fiscal Year	Sex	White	White (%)	More Than One Race	More Than One Race (%)	Unknown / Not Reported	Unknown / Not Reported (%)
2022	Female	2,023	79.2	7	0.3	186	7.3
2022	Male	3,108	80.5	13	0.3	325	8.4
2022	Unknown	4	23.5	0	0.0	13	76.5
2023	Female	1,680	71.3	9	0.4	321	13.6
2023	Male	2,896	77.0	12	0.3	532	14.1
2023	Unknown	4	17.4	0	0.0	19	82.6
2024	Female	5,654	63.9	44	0.5	502	5.7
2024	Male	7,560	71.4	54	0.5	528	5.0
2024	Unknown	6	31.6	0	0.0	11	57.9

Appendix B.3

Table 7. Enrollment for All NIH-Defined Extramural and Intramural Phase III Clinical Trials by Sex and Ethnicity

Fiscal Year	Sex	Not Hispanic	Not Hispanic (%)	Hispanic Latino	Hispanic Latino (%)	Unknown Not Reported	Unknown Not Reported (%)
2022	Female	2,245	87.9	107	4.2	201	7.9
2022	Male	3,257	84.4	256	6.6	348	9.0
2022	Unknown	4	23.5	0	0.0	13	76.5
2023	Female	1,945	82.6	73	3.1	337	14.3
2023	Male	3,043	80.9	160	4.3	559	14.9
2023	Unknown	4	17.4	0	0.0	19	82.6
2024	Female	6,440	72.8	1,079	12.2	1,326	15.0
2024	Male	7,984	75.4	1,407	13.3	1,201	11.3
2024	Unknown	4	21.1	0	0.0	15	78.9

3. Appendix C: Age Data Based on Inclusion Enrollment Records (IERs)

Appendix C.1

Table 8. Age Distribution Using Broad Age Groups for NIH-Defined Extramural and Intramural Clinical Research Reported for Fiscal Years 2022 -2024

Fiscal Year	Children <18 Years (%)	Adults 18-64 years (%)	Older Adults 65+ years (%)	Unknown or Not Reported	Total
2022	8,934 (20.2%)	22,212 (50.3%)	7,747 (17.6%)	5,244 (11.9%)	44,137 (100%)
2023	14,523 (15.9%)	52,966 (58.2%)	20,579 (22.6%)	3,006 (3.3%)	91,074 (100%)
2024	14,560 (15.7%)	39,637 (42.8%)	29,939 (32.3%)	8,459 (9.1%)	92,595 (100%)

4. Appendix D: Total Inclusion Data Records (IERs): All NIH-Defined Phase III Trials

Appendix D.1

Table 9. Valid Analysis* Requirements for NIH-Defined Phase III Extramural and Grants Reported Between Fiscal Years 2022 and 2024

Fiscal Year	Total IERs	IERs Requiring Race Ethnicity Valid Analysis	% IERs Requiring Race Ethnicity Valid Analysis	IERs Requiring Sex Valid Analysis	% IERs Requiring Sex Valid Analysis
2022	23	23	100.0	23	100.0
2023	21	21	100.0	21	100.0
2024	27	26	96.3**	26	96.3

Current methodology to monitor valid analysis began in 2019 and differs from what was used in 2018 (N/A in 2018). Plans for valid analysis methodologies specified in the project application are reported for all IERs, including IERs that have no reported actual enrollment at the time of reporting.

*Valid Analysis: *An unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are: allocation of study participants of both sexes (males and females) and from different racial and/or ethnic groups to the intervention and control groups by an unbiased process such as randomization; unbiased evaluation of the outcome(s) of study participants; and use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects by sex, race, and/or ethnicity. See:* https://grants.nih.gov/policy-and-compliance/policy-topics/inclusion/women-and-minorities/analyses

**A Phase III trial that did not require a valid analysis was included in error. The total number of IERs requiring valid analysis is 26. This correction will be reflected in the 2025 dataset.

5. Appendix E: URL to data by Research Condition and Disease Categorization (RCDC)

Inclusion enrollment data by Research Condition and Disease Categorization (RCDC) category will be available on the RCDC Inclusion Statistics Report website (https://report.nih.gov/RISR/) at a later date but are available by request. These data will now be published annually at this website.