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 FY2019 – FY2021

National Institutes of Neurological Disorders and Stroke (NINDS)

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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.

Healthy People 2020 defines health disparity as "a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion."

The National Institutes of Health (NIH) has designated several U.S. populations that experience Health disparities (e.g. American Indians/Alaska Natives, Asian Americans, Blacks/African Americans, Hispanics/Latinos, Native, Hawaiians and other Pacific Islanders, sexual and gender minorities, socio-economically disadvantaged populations, and underserved rural populations) and are in need of effective tailored prevention and treatment approaches (https://www.nimhd.nih.gov/about/overview/). Poorer 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 (https://www.ninds.nih.gov/About-NINDS/Office-Global-Health-and-Health-Disparities).

Description of NINDS portfolio

NINDS places a high priority on understanding and addressing disparities across the broad spectrum of neurological disorders among racial, ethnic, and other minoritized populations in the United States. The largest part of the NINDS disparities portfolio addresses stroke and cerebrovascular disease, including vascular cognitive impairment and dementia (VCID), for which disparities in incidence, mortality, and functional outcomes have been identified, and for which barriers to proven preventive approaches may exacerbate the disparities. The NINDS extramural program supports 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. NINDS 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, and Alzheimer's Disease and Alzheimer's Disease Related Dementias (AD/ADRD) research. In addition to these high profile/high priority programs, the NINDS continues to address unanticipated public health challenges and scientific opportunities of the pain-opioid crisis, the disparate neurologic impact of the COVID-19 pandemic, and potential long-term sequalae of SARS COVID-19 (PASC) infection, through engagements with research partners across the NIH.

1. Extramural Epidemiological Studies (Select)

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

REGARDS is an observational study designed to understand the disproportionate burden of stroke and cognitive decline among Blacks/African Americans in the United States as well as among individuals residing in the Southeastern United States, a region known as the "Stroke Belt". Between 2003-2007, 30,239 Black/African American and White participants age 45+ across the continental U.S. were recruited with the objective of understanding these racial and geographic disparities as well as the relationship between stroke and, more recently, dementia. Renewed in 2019, AD/ADRD funds were used to leverage and expand the scope of the study to examine several measures related to cognitive decline and dementia in this aging cohort. Following a baseline in-home examination, this cohort continues to be followed for stroke events and cognitive decline. A second in-person assessment has recently been completed to assess incident risk factors for stroke. REGARDS has been a rich source of data on differential risk of stroke and impact of stroke risk factors among African Americans and Whites. A recent publication from this cohort examined the impact of diet on racial differences in developing hypertension. Hypertension is a major U.S. health disparity and the largest modifiable risk for stroke. Ongoing studies are focusing on racial patterns in incident and prevalent cognitive impairment, with the goal of identifying social, cardiovascular, and environmental mechanisms of racial and geographic disparities in vascular cognitive impairment and dementia.

b. Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS):

The Greater Cincinnati/ Northern Kentucky Stroke Study (GCNKSS) is a population-based surveillance study and epidemiologic cohort that has been instrumental in our understanding of racial disparities in stroke incidence and mortality. Over the past 24 years, nearly 20,000 incident stroke cases have been identified and characterized, yielding a powerful source of information that has identified disparities in stroke incidence over time between Whites and Blacks/African Americans and has highlighted an increasing Black/African American/White stroke disparity; this study showed that despite overall declines in stroke incidence, the gap between African Americans and Whites has actually increased. Evaluation of these disparities are ongoing.

c. Northern Manhattan Study (NOMAS): Risk Factors for Stroke and Cognitive Decline in a Tri-Ethnic Region

Funded since 1993, NOMAS is designed to investigate the risk and determinants of stroke, cognitive impairment, and other vascular outcomes in different race-ethnic groups and to help fill gaps in our knowledge of health disparities for stroke and vascular disease in minoritized populations. NOMAS contains the largest Hispanic population cohort (51%) of any NINDS-active prospective study cohorts and focuses on understanding the risk factors for stroke and cognitive decline. The randomly sampled cohort of nearly 3,500 White, Black/African American and Caribbean Hispanic adults living in Northern Manhattan is the first prospective cohort study to focus on vascular risk factors in a multi-ethnic community. The cohort has now been followed for over 20 years. Among many key findings was the identification of race-ethnic differences in risk factor prevalence and impact, information that is critical to the implementation of stroke prevention programs. Although NOMAS was originally focused on stroke, the aging of the cohort has expanded the study's ability to investigate the incidence and risk factors related to declining cognitive trajectories, disability and reduced quality of life, and dementia. Moreover, the continued accumulation of outcome events permitted the advanced study of predictors of ischemic stroke subtypes that vary by race-ethnic group. Since 1993, this cohort has made fundamental contributions to the understanding of vascular risk factors of cognitive impairment and dementia.

2. 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 400 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. StrokeNet has created a Minority Recruitment, Retention and Diversity Committee to assist in the development of strategies to address women and minority recruitment needs. Examples of NIH StrokeNet trials, including their enrollment targets, are as follows:

i. 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 will 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. The target enrollment for CREST-2 is 2,480 participants, 1,200 in each study, 589 in each treatment group, with pre-specified gender/minority targets of 40% for women and 12% for minorities, with further recruitment goals of 17% Hispanics, 9.5% African Americans, 2% Asians and a smaller percentage of other racial minorities. This study is still ongoing and will not have primary analysis for several more years. However, the study team is implementing efforts to increase enrollment of women and race/ethnic minorities, with the intention of conducting comparative analysis of treatment effect.

ii. 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 target enrollment for the trial is 1100 patients with pre-specified gender/minority targets of 50% for women, 13.5% Hispanics, 16.4% black or African American, 6.6% Asian, 0.5% Native American or other Pacific Islander, 0.5% American Indian or Alaska Native, and 7.8% more than one race. This study is still recruiting with about 35% of the cohort remaining.

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

In the almost 20 years since its approval, intravenous tissue plasminogen activator (IV t-PA) remains the only approved medical 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 will compare two promising add-on drugs, Eptifibatide and Argatroban, when combined with t-PA will further reduce disability following an acute ischemic stroke. The target enrollment is a

maximum of 1200 patients with pre-specified gender/minority targets of 48% women, 7% Hispanics, 21.5% black or African American, 6.7% Asian, 0.5% Native American or other Pacific Islander, 0.5% American Indian or Alaska Native, and 1% more than one race. The study is currently ongoing with approximately a quarter of the cohort recruited.

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 11 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. Primary aims of this trial are to select, in patients with severe TBI, the combination of HBO2 treatment parameters that is most likely to demonstrate improvement in the outcome of severe TBI patients in a subsequent phase III trial. HOBIT will enroll consecutive eligible patients with TBI in the racial, ethnic, and gender distributions in which they present to clinical centers. The clinical centers are geographically dispersed across the U.S. and serve racially and ethnically diverse communities. As such, enrollment of subjects is anticipated to reflect that diversity. Eligibility for entry into the trial will not be influenced by race, ethnicity, or gender. For communities with large minority populations that are non-English speaking, consent and enrollment will be achieved by utilizing the appropriate translators and language-specific informed consent documents, as determined by their local IRB's. Participants will only be excluded from the trial on the basis of language if the consent process is precluded because appropriate medical translation for the particular language cannot be made available in the required time window. Race, ethnicity, and gender 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.

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. Another approach is to monitor the partial pressure of oxygen in brain tissue (PbtO2) and apply interventions to prevent brain tissue hypoxia and improve neurologic outcome. Clinical studies demonstrate that brain tissue hypoxia is common, that there is a strong relationship between low PbtO2 and poor outcome, and that timely interventions can reverse brain tissue hypoxia. BOOST-3 trial proposes to 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 gender 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 ethnic distribution of participants in this trial will be similar to the communities served by the trauma centers participating in the study. 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.

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 outcome, 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 will enroll comatose adult survivors of out-of-hospital cardiac arrest that have already been rapidly cooled using a definitive temperature control method. Those with and without initial shockable rhythms will be studied as distinct populations (maximum of 1800 participants over four years). ICECAP will determine if identifying an optimal duration of cooling can improve outcomes, and if development of a duration response curve can substantiate efficacy in a wider patient population. Women will be included in this study, and gender 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 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.

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. Similar to NIH StrokeNet, NeuroNEXT has created a Minority Recruitment, Retention and Diversity Committee to assist in the development of strategies to address women and minority recruitment needs. These committees proactively work with study teams to develop and review plans to allow for maximum study accrual, retention, and diversity. Committee members have also led educational presentations on recruitment strategies, data collection, reporting, and methods to enhance diversity 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.

d. Pediatric Studies (Select)

i. High-dose Erythropoietin for Asphyxia and Encephalopathy (HEAL)

Perinatal hypoxic-ischemic encephalopathy (HIE) occurs in 1-3 per 1,000 term births. Currently, therapeutic hypothermia (HT) is the standard of care for infants with HIE but nearly half of the infants in HT clinical trials either died or suffered moderate to severe neurologic disabilities including long-term motor and cognitive dysfunction. HIE also results in new cases of cerebral palsy (CP). Therefore, there is a strong interest in developing new complementary therapies. The PI team identified erythropoietin (Epo) as a novel neuroprotectant in preclinical models. There are also smaller clinical trials that have confirmed this positive impact. The team's phase I and II trials demonstrated safety, feasibility, desirable pharmacokinetics, and beneficial outcomes as measured by early MRI, biomarkers, 6 month and 2-year outcomes (even among infants with significant brain injury seen on MRI). The team conducted a multicenter, randomized, double-masked, placebo-controlled Phase III neuroprotection trial to test the efficacy of high dose Epo for HIE. They hypothesized that high dose Epo given to cooled infants with moderate/severe HIE will reduce the primary outcome of death or neurodevelopmental impairment at age 22-26 months from 49% to 33%. They further hypothesized that neonatal Epo will be safe, will decrease brain injury severity on neonatal MRI, and will decrease serial inflammatory cytokines and biomarkers of brain injury. The study completed recruitment and was fully

enrolled (501 subjects: 45% females, 24% Hispanic, 13% Black or African American, 7% Asian) in October 2019. The final follow-up visit in the study is expected before January 2022.

ii. MRI-based quantitative brain oxygen metabolism identifying high risk of infarct recurrence in sickle cell anemia

The overall goal of this work is to expand our understanding of the basic pathophysiology of neurological morbidity in sickle cell anemia (SCA) using novel MRI-derived measures of oxygen extraction fraction (OEF). SCA is a well-characterized monogenetic disorder with an abnormal form of hemoglobin (Hb) S that primarily affects Blacks and Africans Americans and leads to many complications including a high prevalence of cerebral vasculopathy, silent cerebral infarcts, and overt strokes, which is 100-fold greater than in other children. Secondary prevention of recurrent cerebral infarcts in children with SCA includes monthly blood transfusion therapy indefinitely. This strategy significantly reduces the risk of recurrent overt and silent strokes but with substantial transfusion-related morbidity. Many children must be transfused to prevent one recurrent infarct. Improved abilities are required to identify and stratify children at the highest risk of stroke. The critical barrier include a general inability to identify underlying brain tissue-level impairment that may provide evidence-based biomarkers for stroke risk. Hemodynamic failure, measured by increased OEF (the ratio of oxygen consumed to oxygen delivered) in the brain, is associated with increased stroke risk. Limited widespread availability of methodologies for measuring OEF has prevented evaluation of OEF rigorous clinical studies in children with SCA at risk of infarct recurrence. The research team demonstrated an ability to utilize MRI to measure OEF noninvasively. They then applied this method in children with SCA to test fundamental hypotheses about the relationships between OEF, other hemodynamic factors such as cerebral blood flow, and cerebral infarcts. The study is in its last year (some goals delayed by the COVID-19 pandemic) but enrollment is complete (105 total participants, 55% female, 100% Black or African American, 0% Hispanic).

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

Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD) disproportionately impact Black/African Americans, Latinos and women. Much of the research into AD/ADRDs, however, does not adequately include these populations or address related disparities. In close collaboration with the National Institute on Aging (NIA), NINDS leads several efforts and initiatives to address health disparities and equity as well as enhance the inclusion of underrepresented populations in AD/ADRD research. Strategic priorities and milestones for NINDS's HD/HE efforts are refined every three years in the ADRD Summit. Last held in 2019, the Summit, which invited extensive input from diverse researchers and public stakeholders, resulted in eight new or revised research milestones that fell under four overarching themes: 1) Assessment of Dementia in Diverse Populations, 2) Resolve AD/ADRD Health Disparities by Discovering Culturally Appropriate Pathways to Effective Prevention and Treatments, 3) Monitor Changes in AD/ADRD Disparities, and 4) Ensure

a Diverse and Inclusive AD/ADRD Workforce. Selected examples of NINDS-supported research projects that are responsive to the health equity/disparities research milestones include:

i. **Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on Recovery (DISCOVERY)**

The DISCOVERY Network is a landmark study to determine the specific subsets of stroke events that cause (and do not cause) cognitive impairment and dementia in post-stroke populations in the United States, with a special focus on populations that experience health disparities. The long-term goal of this study is to identify potential targets for personalized medicine and dramatically reduce the rates of cognitive and functional disability following stroke in high-risk U.S. populations.

ii. **Diverse VCID**

Diverse VCID is prospective clinical research study of patients, particularly those from underrepresented groups, that exhibit incidental white matter lesions found on neuroimaging and who present with cognitive complaints, who thus are at risk for cognitive decline. This project will use advanced brain imaging and blood-based techniques to understand how vascular changes in late life cause brain injury and cognitive decline.

iii. **The Consortium for Detecting Cognitive Impairment, Including Dementia (DetectCID)**

Launched in 2017, DetectCID is a collaborative network of research programs supported by NINDS and NIA that are performing cross-site validation of screening tools to detect cognitive impairment in primary care and other everyday clinical settings, as well as cognitive care and clinical follow-up. Up to half of the funded consortium research focuses on approaches that are specifically designed to address barriers to detecting cognitive impairment in underserved populations.

f. HEAL-EPPIC-NET

The NIH HEAL (Helping to End Addiction Long-term) Initiative focuses efforts on advancing scientific solutions for the opioid crisis, improving prevention and treatment of opioid misuse/addiction, and enhancing pain management. NINDS established the Early Phase Pain Investigation Clinical Network (EPPIC-Net) to accelerate and enhance clinical testing of novel, non-addictive pharmacologic and non-pharmacologic therapeutics ("assets") targeted to pain conditions of high unmet need, and evaluate new as well as repurposed small molecules, biologics, natural products, and devices. EPPIC-Net conducts cutting-edge early phase clinical trials of pain therapeutics submitted by industry, academic, and other partners across the age and pain condition spectrum. EPPIC-Net provides investigators with access to an early-phase pain research network with expert infrastructure providing study design, conduct, and analysis at no cost to the asset provider. The

EPPIC-Net program recognizes the importance of recruiting a diverse and inclusive patient population. Investigators include those with expertise in enhancing diversity to ensure inclusive patient populations. This is a charge of the Network and will be a part of the recruitment plans for each funded trial. EPPIC-Net's first trial opened for recruitment in November 2021.

g. COVID-19 Neuro Database-BioBank

This databank/biobank, supported by NINDS and run by New York University, collects information on new neurological symptoms in patients with confirmed COVID-19 as well as exacerbation of pre-existing neurological conditions. Data from adults, children, and neonates with confirmed COVID-19 infection is submitted by partners nationally and internationally. Pregnant women are included so that pregnancy outcomes and effects on infants with in-utero exposure can be assessed. The biobank accepts a wide variety of bio-samples, including blood, plasma, cerebrospinal fluid, and tissue from these patient cohorts. All specimens will be pre-existing; no specimens are collected specifically for this project. Samples do not need to be submitted to the biobank for storage. Rather, the database can track the availability of samples for participants that are stored at other repositories. The COVID-19 Neuro Databank/Biobank makes data and samples available to researchers to better understand how COVID-19 affects the nervous system.

h. 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 recently diagnosed people with Parkinson's disease (PD). If successful, this study will have a significant impact on the quality of life of people with PD and their caregivers as well as public health since it will 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. Each study site will implement extensive outreach programs to make sure that the study recruits its targeted enrollment sample. 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.

3. 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.

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 by sex/gender, race, and ethnicity 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 sex/gender, 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 the Scientific Review Group (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/gender 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/gender and race/ethnicity analyses in applications and annual progress reports.

Grants management staff monitor the human subjects' system and reporting (HSS) module for discrepancies and 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

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 IRB reviews intramural research protocols for compliance with inclusion guidelines and conducts annual monitoring. With each annual review and renewal, the investigator documents the number, gender, 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. Additionally, the Office of Scientific Director reviews all proposed salaries for scientific staff to ensure equity, the diverse representation of our faculty on all IRP committees and taskforces, and diversity in the Porter Neuroscience Seminar Series speakers (as well as the planning committee itself). Lastly, the IRP ensures that all search committees include members who are women and minorities; it also engages with the NIH Office of Equity, Diversity and Inclusion and utilizes NINDS internal recruitment strategists to ensure that all scientific staff recruitments reach out to, and result in, a diverse applicant pool.

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

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 diverse populations, and reducing accrual barriers in these under-represented communities. The DCR 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 diverse race/ethnic groups. In

2021, a DCR workgroup was created to review and implement best practices.

In addition to the strategies to ensure compliance, the clinical trials division developed and employs a series of NIH inclusion policy monitoring tools. The most useful is an internal enrollment tracking system that allows trial sites to submit real-time accrual data, the Recruitment Planning and Monitoring System (RPMS). Through the use of this database, Program staff can track gender, race, ethnicity, individualize reports, and compare target enrollment with actual enrollment for inclusion tracking.

Also, NINDS provides support for Networks and individual trial efforts to identify and overcome enrollment barriers. NINDS Program staff draft plans 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 network-specific Minority Recruitment, Retention and Diversity Committees to assist in the development of strategies to address women and minority recruitment needs in their portfolios. The committees proactively work with study teams to develop and review plans to allow for maximum study accrual, retention, and diversity.

Committee members have also led educational presentations on recruitment strategies, data collection, reporting, and methods to enhance diversity 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. The NINDS Office of Global Health and Health Disparities (OGHHD) within the Division of Clinical Research, in collaboration with the NINDS Office of Science Policy and Planning (OSPP) is developing a comprehensive health equity strategic plan that will include strategies for educating NINDS staff about community engage, diversity recruitment and the inclusion of diverse participants in clinical trials. An NINDS specific health equity workgroup (HEW) has been created as a platform to provide this education and training.

III. Analysis and Interpretation of Data

A. Summary of the inclusion data for the required tables

As shown in Table 1, in 2019 the NINDS received 835 inclusion enrollment reports (IERs); 880 IERs in 2020 and 974 in 2021. These numbers are divided into studies with and without enrollment; US and non-US sites; and single gender enrolling studies per annum. There is no significant difference in these numbers except for a slight increase in IERs from non-US sites in 2021.

Table 2 reveals the numbers of individuals enrolled in NIH defined clinical trials per annum categorized by sex/gender and minority status. 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. Also noted in this table, there is a slight increase in the "Unknown" category FY20, this is due in part to the addition of IERs involving de-identified research samples and patient records lacking data on sex/gender and race/ethnicity.

Tables 3 and 3.1 categorizes all individuals enrolled at NINDS in NIH defined clinical trials by sex/gender and race and in Table 4 by ethnicity. During this time-period, there is no significant change in the enrollment numbers by sex/gender or race. However, there is a slight increase in the ethnicity numbers in 2020 and 2021, based on the addition of an international study in a Latin country.

Table 5 displays the number of individuals enrolled in all NIH defined phase III clinical trials at NINDS by sex/gender; Tables 6 and 6.1 displays this information by sex/gender and race; and Table 7 displays this information by sex/gender and ethnicity. Across this three-year period, there is no significant change in the enrollment numbers based on these criteria for phase III clinical trials, except for a slight increase in Hispanic/Latino enrollment in 2020 due in part to the international enrollment.

Table 8 reveals the age distribution of individuals enrolled in clinical studies at NINDS in 2021 using broad categories. This information was not systematically collected prior to 2021 but will be collected and tracked prospectively. All phase III clinical trials that were required to report valid analysis did so, achieving a compliance rate of 100%.

IV. Appendices

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 Extramuraland Intramural Clinical Research Reported Between FY2019 and FY2021

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**
2019	835	235	600	563	37	14	37	549
2020	880	308	572	535	37	17	33	522
2021	974	381	593	550	43	20	27	546

* 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/gender, and combination of unknown and any sex/gender(s)

Appendix A.2

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

Fiscal Year	Sex/Gender	Total Enrollment	Total (%)	Minority Enrollment*	Minority (%)
2019	Female	59,050	49.2	22,814	38.6
2019	Male	58,569	48.8	20,901	35.7
2019	Unknown	2,376	2.0	204	8.6
2020	Female	57,752	46.8	25,993	45.0
2020	Male	58,786	47.6	25,484	43.4
2020	Unknown**	6,925	5.6	4,103	59.2
2021	Female	61,197	49.1	27,325	44.7
2021	Male	61,702	49.5	26,574	43.1
2021	Unknown	1,797	1.4	77	4.3

*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 FY20 is due in part to the addition of IERs involving de-identified research samples and patient records lacking data on sex/gender and race/ethnicity.

Appendix A.3

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

Fiscal Year	Sex / Gender	American Indian / Alaska Native	American Indian / Alaska Native (%)	Asian	Asian (%)	Black / African American	Black / African American (%)	Native Hawaiian / Pacific Islander	Native Hawaiian / Pacific Islander (%)
2019	Female	289	0.5	3,052	5.2	8,873	15.0	78	0.1
2019	Male	237	0.4	3,064	5.2	8,272	14.1	135	0.2
2019	Unknown	1	0.0	26	1.1	100	4.2	1	0.0
2020	Female	316	0.5	4,161	7.2	9,342	16.2	92	0.2
2020	Male	322	0.5	3,991	6.8	8,880	15.1	140	0.2
2020	Unknown	0	0.0	22	0.3	60	0.9	0	0.0
2021	Female	295	0.5	3,817	6.2	8,859	14.5	106	0.2
2021	Male	263	0.4	3,469	5.6	8,914	14.4	116	0.2
2021	Unknown	11	0.6	21	1.2	15	0.8	0	0.0

Appendix A.3.1

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

Fiscal Year	Sex / Gender	White	White (%)	More Than One Race	More Than One Race (%)	Unknown / Not Reported	Unknown / Not Reported (%)
2019	Female	36,267	61.4	1,715	2.9	8,776	14.9
2019	Male	36,495	62.3	1,532	2.6	8,834	15.1
2019	Unknown	542	22.8	3	0.1	1,703	71.7
2020	Female	34,326	59.4	1,354	2.3	8,161	14.1
2020	Male	35,244	60.0	1,260	2.1	8,949	15.2
2020	Unknown	4,073	58.8	4	0.1	2,766	39.9
2021	Female	38,399	62.7	1,357	2.2	8,364	13.7
2021	Male	38,448	62.3	1,186	1.9	9,306	15.1
2021	Unknown	87	4.8	4	0.2	1,659	92.3

Appendix A.4

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

Fiscal Year	Sex / Gender	Not Hispanic	Not Hispanic (%)	Hispanic Latino	Hispanic Latino (%)	Unknown Not Reported	Unknown Not Reported (%)
2019	Female	42,452	71.9	10,323	17.5	6,275	10.6
2019	Male	42,284	72.2	8,916	15.2	7,369	12.6
2019	Unknown	683	28.7	81	3.4	1,612	67.8
2020	Female	40,066	69.4	11,546	20.0	6,140	10.6
2020	Male	39,865	67.8	11,611	19.8	7,310	12.4
2020	Unknown	206	3.0	4,021	58.1	2,698	39.0
2021	Female	42,156	68.9	13,643	22.3	5,398	8.8
2021	Male	41,766	67.7	13,430	21.6	6,596	10.7
2021	Unknown	168	9.3	27	1.5	1,602	89.1

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/Gender

Fiscal Year	Sex/Gender	Total Enrollment	Total (%)	Minority Enrollment	Minority (%)
2019	Female	2,175	41.3	840	38.6
2019	Male	3,084	58.6	1,027	33.3
2019	Unknown	2	0.0	0	0.0
2020	Female	2,324	42.3	903	38.9
2020	Male	3,170	57.7	1,180	37.2
2020	Unknown	2	0.0	0	0.0
2021	Female	1,893	41.9	357	18.9
2021	Male	2,623	58.0	425	16.2
2021	Unknown	6	0.1	0	0.0

Appendix B.2

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

Fiscal Year	Sex / Gender	American Indian / Alaska Native	American Indian / Alaska Native (%)	Asian	Asian (%)	Black / African American	Black / African American (%)	Native Hawaiian / Pacific Islander	Native Hawaiian / Pacific Islander (%)
2019	Female	10	0.5	61	2.8	516	23.7	6	0.3
2019	Male	20	0.6	91	3.0	587	19.0	19	0.6
2019	Unknown	0	0.0	0	0.0	0	0.0	0	0.0
2020	Female	14	0.6	51	2.2	431	18.5	9	0.4
2020	Male	23	0.7	86	2.7	481	15.2	17	0.5
2020	Unknown	0	0.0	0	0.0	0	0.0	0	0.0
2021	Female	6	0.3	23	1.2	212	11.2	4	0.2
2021	Male	15	0.6	62	2.4	181	6.9	9	0.3
2021	Unknown	0	0.0	0	0.0	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/Gender and Race – continued

Fiscal Year	Sex / Gender	White	White (%)	More Than One Race	More Than One Race (%)	Unknown / Not Reported	Unknown / Not Reported (%)
2019	Female	1,449	66.6	21	1.0	112	5.1
2019	Male	2,224	72.1	17	0.6	126	4.1
2019	Unknown	2	100.0	0	0.0	0	0.0
2020	Female	1,714	73.8	11	0.5	94	4.0
2020	Male	2,454	77.4	15	0.5	94	3.0
2020	Unknown	2	100.0	0	0.0	0	0.0
2021	Female	1,534	81.0	39	2.1	75	4.0
2021	Male	2,211	84.3	32	1.2	113	4.3
2021	Unknown	4	66.7	0	0.0	2	33.3

Appendix B.3

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

Fiscal Year	Sex / Gender	Not Hispanic	Not Hispanic (%)	Hispanic Latino	Hispanic Latino (%)	Unknown Not Reported	Unknown Not Reported (%)
2019	Female	1,857	85.4	244	11.2	74	3.4
2019	Male	2,689	87.2	311	10.1	84	2.7
2019	Unknown	2	100.0	0	0.0	0	0.0
2020	Female	1,784	76.8	488	21.0	52	2.2
2020	Male	2,424	76.5	687	21.7	59	1.9
2020	Unknown	2	100.0	0	0.0	0	0.0
2021	Female	1,720	90.9	78	4.1	95	5.0
2021	Male	2,340	89.2	133	5.1	150	5.7
2021	Unknown	4	66.7	0	0.0	2	33.3

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 Year 2021

Fiscal Year	Children (<18 years)	Adults (18-64 years)	Older Adults (65+ years)	Unknown or Not Reported	Total
2021	4,351	2,682	2,403	19	9,455
	46.0%	28.4%	25.4%	0.2%	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 Intramural Grants Reported Between Fiscal Years 2019 and 2021

Fiscal Year	Total IERs	IERs Requiring Race Ethnicity Valid Analysis	% IERs Requiring Race Ethnicity Valid Analysis	IERs Requiring Sex Gender Valid Analysis	% IERs Requiring Sex Gender Valid Analysis
2019	17	17	100.00	17	100.00
2020	27	27	100.00	27	100.00
2021	19	19	100.00	19	100.00

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/genders (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/gender, race, and/or ethnicity. See: https://grants.nih.gov/policy/inclusion/women-and-minorities.htm*

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

Inclusion enrollment data by Research Condition and Disease Categorization (RCDC) category for FY2021 will be available at this URL : https://report.nih.gov/RISR/ after March 1, 2022.