



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
FY2016 – FY2018

National Institutes of Neurological Disorders and
Stroke (NINDS)

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NINDS Report Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities in Clinical Research as Reported in FY2016 – FY2018

I. Background/Overview

A. Mission statement

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease.

This burden is borne by every age group, every segment of society, and people all over the world. Most disorders of the nervous system affect men and women equally, but certain disorders, such as epilepsy, Rett syndrome (RTT), stroke, traumatic brain injury (TBI), multiple sclerosis (MS), chronic pain, and migraines disproportionately affect women, or have specific health implications for women. NINDS supports basic, translational, and clinical research on these disorders, as well as targeted research to understand sex-based differences in normal development and function of the nervous system, behavior, cognition, and perception.

B. 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 minority populations in the United States. The largest part of the NINDS disparities portfolio addresses stroke and cerebrovascular disease, including vascular cognitive impairment and dementia, for which disparities in incidence, mortality, and functional outcomes have been identified, and for which barriers to proven preventive approaches may exacerbate the disparities. Through its extramural program supporting epidemiologic and genetic studies as well as clinical trials, patterns of health disparities and effects of intervention are studied.

1. Extramural Studies

The following are examples of NINDS extramural studies reporting enrollment of participants during 2016-2018. Studies are grouped by disorder/disease. Stroke studies are further grouped by whether they were epidemiological studies or Phase 3 clinical trials, and whether they were conducted through one of our trial networks, NeuroNEXT or StrokeNet.

a. Epilepsy

Established Status Epilepticus Treatment Trial (ESETT): Status epilepticus (SE), consisting of prolonged seizures, is a neurological emergency that can result in brain injury or even death. Patients in SE are initially treated with benzodiazepines, but approximately 33% do not respond to these drugs. These patients are considered to have established SE (ESE). The ESETT treatment trial is designed to determine the most effective and/or the least effective treatment of ESE among patients older than 2 years by comparing three arms: fosphenytoin (fPHT) levetiracetam (LVT), and valproic acid (VPA). This is a multicenter, randomized, double-blind, Bayesian adaptive, phase 3 comparative

effectiveness trial¹. SE occurs more commonly in the African American population. Thus, this study expects that more patients of that race will be enrolled overall. This study is ongoing and has a planned enrollment of 795 participants (49% females, 13% Hispanics, 49% African Americans, 5% Asians and a small population of other racial minorities).

b. Stroke

Epidemiological Studies

Reasons for Geographic And Racial Differences in Stroke (REGARDS): REGARDS is an observational study designed to understand the disproportionate burden of stroke and cognitive decline among 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 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 dementia. 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, including a recent publication on racial differences in the role of diet in the risk of developing hypertension², which is the largest contributor to risk of stroke. A newly established substudy will focus 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 incident vascular cognitive impairment and dementia.

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 African Americans and has highlighted an increasing 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. Beginning with the current funding period, additional studies looking at stroke recurrence as well as outcomes have contributed to the literature on stroke disparities.

Risk Factors for Stroke and Cognitive Decline in a Tri-Ethnic Region: Northern Manhattan Study (NOMAS): 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 minority populations. The randomly sampled cohort of nearly 3,500 White, 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 a median of nearly 20 years. Among many key findings was the identification of race-ethnic differences in risk factor prevalence and impact, information that is critical to implementation of stroke prevention programs.

NOMAS has discovered several key disparities, including that: i) the incidence of stroke due to intracranial atherosclerosis was significantly higher in African Americans and Hispanics compared to Whites³; ii) maximum carotid plaque thickness ≥ 1.9 mm was a more potent predictor of risk of vascular events in Hispanics than in Whites and African Americans⁴; and iii) adiponectin, an adipocytokine secreted from adipose tissue that is thought to have an inverse association with vascular risk factors, was lower among African Americans and Hispanics and those with various vascular risk factors⁵.

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 will permit the advanced study of predictors of ischemic stroke subtypes that vary by race-ethnic group.

Brain Attack Surveillance in Corpus Christi (BASIC): BASIC is a community-based stroke surveillance study that was established in 1999 to characterize the relative stroke burden in Mexican American and non-Hispanic White populations in Corpus Christi, Texas. Since its inception, BASIC has identified and validated over 11,000 acute cerebrovascular events, which are being tracked for recurrence and outcomes. Findings from nearly 20 years of data have shown overall declines in stroke rate but increasing stroke incidence in older Mexican Americans, as well as a continued disparity in recurrence, with Mexican Americans nearly 40% more likely to experience a second stroke within a year. Some findings of this study that are important to highlight are: Women had lower overall stroke quality of care than men⁶, Mexican Americans (MA) receive less intensive stroke rehabilitation than non-Hispanic Whites⁷, there were no ethnic differences in the overall quality of stroke care between MAs and non-Hispanic Whites (NHW)⁸, more than two-thirds of MA stroke patients had sleep-disordered breathing, which was 40% more common than in NHW⁹ and the higher prevalence of diabetes mellitus and hypertension and stronger association of diabetes mellitus with ischemic stroke among midlife MAs likely contribute to persistent midlife ethnic stroke disparities¹⁰.

Stroke Prevention-Intervention Research Program (SPIRP): The NINDS-supported SPIRP was established in 2012 to support regional programs to address culturally tailored interventions that involve stroke disparities in different populations. Four regional consortia – in San Francisco, Los Angeles, New York City, and Miami – developed and evaluated scientifically sound interventions to address health disparities in stroke in minority communities in the US using effective and culturally appropriate methods. Studies conducted within this program included evaluation of educational approaches to improve stroke literacy among minorities; comparative effectiveness of home blood pressure telemonitoring; and approaches to risk factor management (e.g. utilizing community health workers).

Phase 3 Clinical Trials

Stroke Network (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 29 regional recruitment coordinating centers that include over 400 stroke hospitals across the U.S. StrokeNet serves as the primary infrastructure and pipeline for testing new potential treatments for patients with stroke and those at risk for stroke.

EnDovascular ThErapy Following Imaging EvalUation for ISchemic Stroke 3 (DEFUSE 3): DEFUSE 3 was a phase 3 clinical trial designed to evaluate the efficacy of mechanical clot removal (thrombectomy) compared with medical management in selected patients with acute ischemic stroke. The study found that endovascular thrombectomy for ischemic stroke 6 to 16 hours after a patient was last known to be well plus standard medical therapy resulted in better functional outcomes than standard medical therapy alone among patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion¹¹. DEFUSE 3 had a direct and immediate impact on the management guidelines of stroke and has been recognized by Congress for receiving a Clinical Research Achievement Award. This study was stopped early for overwhelming efficacy in 2017 after enrolling 182 participants (51% females, 13% Hispanics, 8% African Americans, 3% Asians and a small percentage of other racial minorities). Subgroup analysis showed consistent results across gender, race, and ethnicity category.

Stroke Studies initiated before StrokeNet

Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral hemorrhage evacuation (MISTIE III): This was a randomized, controlled, open-label, blinded endpoint phase 3 trial. The study assessed whether minimally invasive catheter evacuation followed by thrombolysis (MISTIE) with the aim of decreasing clot size to 15 mL or less, would improve functional outcome in patients with intracerebral hemorrhage. Results showed that for moderate to large intracerebral hemorrhage, MISTIE did not improve the proportion of patients who achieved a good response 365 days after intracerebral hemorrhage. MISTIE-III randomized 506 participants representing gender, racial and ethnic diversity (17.8% African Americans, 5.9% Asians, 13.4% Hispanics and 39% females)¹². Analysis of the primary outcome included comparisons by race (African American or White), Hispanic ethnicity (Y or N), sex (M or F), and age (<65 or >65). These subgroup comparisons were consistent with the overall results (no treatment benefit).

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 stroke¹³. 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 2,356 participants, 1,178 in each study, 589 in each treatment group, with gender/minority targets of 40% females, 20% Hispanics, 16% African Americans, 3% 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.

Neurological Emergencies Treatment Trials (NETT) Network

NETT was an emergency neurology network that conducted large, pragmatic, phase 3 trials for acute conditions commonly treated in the emergency room. NETT completed 7 large stroke, trauma and epilepsy trials between 2006 and 2018, four of which enrolled more than 1000 participants with broad representation of women and minorities. The following studies were completed between 2016 and 2018:

Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT): This study, which ended in 2018, was a randomized, double-blind trial that compared clopidogrel vs placebo in patients treated with aspirin following initial transient ischemic attack (TIA) or other minor stroke to determine effect on event-free survival. The trial was halted after 84% of the anticipated number of patients had been enrolled because the data and safety monitoring board had determined that the combination of clopidogrel and aspirin was associated with both a lower risk of major ischemic events and a higher risk of major hemorrhage than aspirin alone at 90 days¹⁴, a result that led to changes in practice guidelines. POINT enrolled a total of 4,881 participants (45% females, 8% Hispanics, 19% African American, 3% Asians and a smaller percentage of other racial minorities). Results were consistent across gender/race subgroups.

Stroke Hyperglycemia Insulin Network Effort (SHINE): This study compared intensive glucose therapy via IV insulin vs standard glucose control using insulin shots in acute ischemic stroke patients with hyperglycemia. The study found that intense glucose therapy did not improve 90-day functional stroke outcomes compared to standard glucose control, thus providing clear evidence to guide the control of glucose levels in stroke patients presenting with hyperglycemia. The primary results of the SHINE trial were presented on February 6, 2019 during the International Stroke Conference Plenary Session in Honolulu, Hawaii. SHINE randomized 581 participants to the intensive insulin group and 570 to the standard of care group. The study enrolled to the intensive group 45% females, 15% Hispanics and 31% African Americans. The standard group enrolled a similar population, 46% females, 16% Hispanics, and 27% African Americans¹⁵.

c. Pediatric Trials

Preterm Erythropoietin Neuroprotection Trial (PENUT): Approximately 63,000 infants per year are born at less than 28 weeks of gestation in the US. Cerebral palsy, deafness, blindness, and/or mental retardation are present in 50% of surviving extremely preterm infants at school age. The burden of extreme prematurity to each patient and to society is further magnified by the years of productive life lost. New therapies are needed to improve these outcomes. Recombinant human erythropoietin (Epo) is a promising novel neuroprotective agent. The PENUT Trial is a randomized, multi-center, placebo-controlled phase 3 trial that will assess whether high dose Epo will improve survival without neurodevelopmental impairment in infants born between 24 and 28 weeks of gestation. Infants were enrolled at 16 centers across the U.S. Subjects and are assessed at 2 years of age to see whether Epo treatment will improve neurodevelopmental outcomes. This study completed enrollment at the end of 2018. This study met its target enrollment at 941 participants (48% females, 21% Hispanics, 26% African Americans, 3% Asians and 2% of other racial minorities). Results are expected in early 2020.

d. Parkinson's Disease (PD)

Phase 3 Trial of Inosine for Parkinson's Disease: This is a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial to determine whether oral inosine dosed to moderately elevate serum urate over 2 years slows clinical decline in early PD. Women typically comprise ~35% of early PD populations in clinical trials, and a similar proportion of the general PD population. By contrast, women are projected to represent ~50% of subjects enrolled in the planned study enrollment. Overall, there is no clear expectation of a gender difference in inosine's hypothesized therapeutic effect, and the study was accordingly powered to test the primary hypothesis on men and women together. However, secondary analyses will consider any differences between gender. Urate levels are not known to vary substantially by race (in contrast to gender) and ethnic or racial differences in the effect of inosine are not expected but exploratory analyses to identify differential treatment effects are planned. Past PD studies have enrolled approximately 97% Caucasians, reflecting persistent challenges in minority recruitment. The study team is undertaking measures to ensure recruitment of minority subjects into the study. Enrolling sites include regions and cities with substantial minority populations in addition to public outreach, referrals through a national automated system and patient advocacy groups. The study also has a Recruitment and Retention Committee that will work with sites and other foundations such as The Parkinson Study Group Healthcare Outcomes & Disparities" Working Group. This trial is still ongoing. The target enrollment is 270 participants (50% females, 4% Hispanics, 3% African Americans, 3% Asians and 1% of other racial minorities).

Parkinson's Disease and Dementia P50NS053488-10: The purpose of the NINDS Udall Center of Excellence for Parkinson's Disease Research (P50) is to utilize a multidisciplinary research approach to elucidate the fundamental causes of Parkinson's disease (PD) and in doing so improve the diagnosis and treatment of patients with Parkinson's and related neurodegenerative disorders. The goal of the Udall Center at the University of Pennsylvania was to advance understanding of the etiology of PD

without and with dementia (PDD) as well as dementia with Lewy bodies (DLB). Community outreach and recruitment of diverse cohorts into associated clinical studies is part of the mission of the Udall Center program. One specific aim of the Clinical Core of the Penn Udall Center focused on community outreach efforts that include regional education of physicians and other healthcare providers, people with PD and their families, and traditionally underserved minorities in the Philadelphia region. The latter goal was accomplished by presenting lay audience accessible information at health fairs, senior centers, churches and long-term care facilities. The Administrative Core of the Center also served as an informational resource for the community through social media and outreach events including an annual symposium for the local patient/caregiver community.

2. Intramural Studies

The following NINDS intramural studies reported enrollment of participants during 2016-2018:

a. Multiple Sclerosis

Multiple Sclerosis is the most common, disabling chronic disease of the central nervous system in young adults. Approximately 2.3 million people are affected worldwide, and it is at least 2-3 times more common in women than men.

Manganese-Enhanced Magnetic Resonance Imaging in Healthy Volunteers and People with Multiple Sclerosis (11-N-0116): This is an open label study of a manganese-based MRI contrast agent in multiple sclerosis and healthy volunteers. The study explores whether this imaging method can better-delineate extent of injury and impact on connectivity resulting from inflammation in MS. Up to 10 healthy volunteers and up to 10 patients with MS will be enrolled. This research is ongoing and is the basis for a new clinical trial in collaboration with the NINDS Neuroimmunology Clinic to test whether corticosteroids improve lesion repair.

Integrating Genetic and Environmental Risk Scores into an Algorithm to Predict Multiple Sclerosis Susceptibility (12-N-0122): This is the NIH substudy of the overall GEMS (Genes and Environment in MS) study, a multicenter study investigating the genetic, immune, and neuroimaging profiles that might increase a person's risk of developing multiple sclerosis in order to identify and validate predictive biomarkers of populations at risk for this disorder. The study is a prospective natural history cohort study recruiting subjects with MS and first-degree relatives of people with MS. This study enrolled 100 participants at risk for MS, with 41 at higher risk (40 women [98%]) and 59 at lower risk (25 women [42%]). In analysis limited to female participants, higher-risk asymptomatic family members of patients with MS were more likely to have early subclinical manifestations. These findings underscore the importance of early detection in high-risk individuals¹⁶.

The pathological basis of MRI signal changes in multiple sclerosis: a longitudinal in vivo-to-postmortem study (16-N-0055): This is a longitudinal observational study exploring the natural history of multiple sclerosis over the lifetime of affected patients. Patients willing to donate their brain to science for the purpose of correlating in vivo radiological findings to post-mortem pathology are eligible for participation. This study is currently recruiting participants. Subjects are followed annually with collection of clinical, laboratory and imaging outcomes.

The effect of corticosteroids on inflammation at the edge of acute multiple sclerosis plaques: An investigator-blinded study (16-N-0114): This study is an investigator-blind, placebo-controlled study exploring whether treatment with corticosteroids affects the development of an imaging biomarker found to be associated with chronically inflamed white matter lesions in multiple sclerosis. Chronically inflamed lesions in turn are associated with progression of disability in multiple sclerosis. Thirty subjects will be enrolled, and following randomization, receive either 3 days of corticosteroids or no treatment; subjects are then followed for 25 weeks to determine outcome. This study has a target enrollment of 10 participants and is currently recruiting subjects.

Anakinra for the treatment of chronically inflamed white matter lesions in multiple sclerosis (T-N-4395): This proposed study is an open-label, single-arm, interventional study exploring whether short-term treatment with anakinra, a recombinant form of the human interleukin-1 receptor antagonist, can resolve an imaging marker found to be associated with chronically inflamed white matter lesions in multiple sclerosis. Chronically inflamed lesions are in turn associated with progression of disability in multiple sclerosis. Five patients will be recruited; patients will be treated for up to 12 weeks, and then followed for an additional 12 weeks. This study design was developed based on observations made in the NIH natural history study of MS (89-N-0045, PI: Reich), and is expected to represent a new approach to rapidly screen candidate agents with neuroprotective/neuroreparative effect in this disease.

b. Infectious Diseases

Immuno-virological evaluation of human T cell lymphotropic virus (HTLV) infection and associated neurological diseases (98-N-0047): 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 commonly infection is asymptomatic, however in less than 5% of infected individuals it is 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.

3. BRAIN Initiative

Since FY 2014, NINDS has been a leader of the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. This Initiative aims to develop and apply cutting-edge technologies to create a dynamic picture of the brain in action, providing the critical knowledge base for researchers seeking new ways to treat, cure, and even prevent brain disorders.

BRAIN has many exciting ongoing studies in different neurological areas. One of their ongoing studies is the “Causal mapping of emotion networks with concurrent electrical stimulation and fMRI” study. Emotions are a highly salient aspect of our lives and show prominent individual differences. Disorders of emotion are also one of the most disabling aspects of neurological and psychiatric disease. Yet options for treatment are limited because we do not understand the neural systems by which emotions are processed. One of the aims of this study is to identify differences in gender when mapping for emotion

networks. The study team will quantify individual differences as a function of mood, age, and subject gender. This study will be conducted at the University of Iowa. It is expected that approximately half of the participants will be females. Because of the regional demographic pattern there are very few minority patient-subjects. However, the state has a state-wide indigent care program that enables all patients to be evaluated and treated at the University of Iowa Hospitals and Clinics, so this population will also be included.

4. Health Disparities (HD)

NINDS participated in several trans-NIH initiatives to address health disparities in Alzheimer's disease and Alzheimer's disease related dementia (AD/ADRD). Most of the collaborations were led by the National Institute on Aging (NIA) and many NIH institutes and other federal agencies participated as partners. The mechanisms and NINDS-supported projects are listed below.

RFA-NS-17-012: Detecting Cognitive Impairment, Including Dementia, in Primary Care and Other Everyday Clinical Settings for the General Public and in Health Disparities Populations (UG3/UH3): The purpose of this funding opportunity announcement (FOA) was to invite applications that address the unmet need to detect cognitive impairment, including dementia, in large and diverse populations seen in primary care across the United States, including in health disparities populations, when a patient, relative, or care provider indicates concern.

There are currently 3 grants funded through this mechanism:

- a. **MYCog - Rapid Detection of Cognitive Impairment in Everyday Clinical Settings**: The study team developed a brief, readily available, standard set of cognitive impairment (CI) screening measures applicable for use in diverse settings and with diverse populations. Specific aims of this study are to refine the MyCog paradigm and field test implementation in primary care settings and validate MyCog in primary care settings using an existing cohort of well-characterized, ethnically and racially diverse adults ages 65-85. This study is ongoing and plans to enroll 450 participants, which are expected to include over 50% minorities (50% African Americans, 3% Hispanics, 31% females).
- b. **The UCSF Brain Health Assessment (BHA) for the Detection of Cognitive Impairment among Diverse Population in Primary Care**: This grant will study a user-friendly, brief, neurocognitive screen administered in a tablet interface. This interface has shown in preliminary studies a good combined sensitivity and specificity to assessment of CI among English-speaking older adults with moderate to high levels of education. The primary goals of this study are to optimize and validate the BHA for older adults who are diverse in terms of education and language spoken, to perform cross-validation studies of other paradigms funded by this award, and to evaluate and address barriers to detecting cognitive impairment in primary care. This study is ongoing and plans to enroll 575 participants with a good representation of gender, race and ethnic minorities (14% African American, 60% White, 33% Hispanic, 59% Women).
- c. **5-COG Battery to Improve Detection of Cognitive Impairment and Dementia**: Despite the availability of numerous cognitive assessment tools, CI related to dementia is frequently under-diagnosed in

primary care settings. The investigators have developed a 5-minute cognitive screen (5-Cog) coupled with a decision tree to overcome the technical, cultural and logistic barriers of current cognitive screens to improve dementia care in primary care patients with cognitive concerns. One of the specific aims is to test feasibility of administering the 5-Cog in different ethnic groups, low literacy patient populations as well as in urban and rural sites. This will enable the researchers to standardize procedures as well as identify potential subject flow and personnel issues in implementing the 5-Cog battery in primary care sites. This study is ongoing and is planning to enroll 1,200 participants, all racial and ethnic minorities, approximately 50% females.

PAR-15-349: Health Disparities and Alzheimer's Disease (R01): This FOA invites applications proposing to study health disparities in AD and related disorders. Health-disparities research related to AD should include the study of biological, behavioral, sociocultural, and environmental factors that influence population level health differences. This announcement is a trans-NIH collaboration led by NIA. It expired on January 8, 2019. Thirty new awards were funded from 2016 to 2018. NINDS participated in a shared portfolio, but leads two of the studies:

- a. **Cognitive impairment in Mexican Americans:** a population-based study: Hispanic/Latinos will comprise more than 30% of the U.S. population by mid-century, and Mexican Americans (MA) account for the largest share of this growing segment of society. As the MA population continues to grow and age we must prepare for the medical, social and economic impact of cognitive impairment and dementia in this large minority population¹⁷. The aims of the study are to use door-to-door surveillance in Nueces County, Texas, a non-immigrant, bi-ethnic community, to determine the prevalence and trajectory over time of cognitive impairment and dementia, to study the amount, distribution and characteristics of informal caregiving for dementia, to determine the community resources most needed by patients and families to care for those with cognitive impairment and dementia. Mexican Americans will be compared with non-Hispanic Whites. This study reported its first Inclusion Enrollment Report in 2017. It is still too early for an analysis of the results. The target enrollment of this study is 2,100 participants, 50% MAs and 50% non-Hispanic Whites.
- b. **The Effect of Lower Blood Pressure Over the Life Course on Late-Life Cognition in Blacks, Hispanics, and Whites (BP-COG):** There is a fundamental gap in understanding how racial/ethnic differences in control of blood pressure (BP) influence racial/ethnic disparities in cognitive impairment and dementia (CID). The objectives of this study are to quantify the effects of racial/ethnic differences in BP control on disparities in CID, to quantify the potential impact of optimal BP treatment intensity to reduce these disparities, and to identify potential interventions for a future trial to reduce the risk of CID or cognitive decline. This study will analyze data from 6 ongoing longitudinal, population-based cohorts and expects to include data for 30,750 participants (21% African Americans, 6% Hispanics, 55% females).

5. NINDS Participating to Encourage Health Disparities Research in ADRD

During the Alzheimer's Disease-Related Dementias (ADRD) Summit of 2016¹⁸, the following milestones were drafted to improve Health Disparities, Inclusion and Recruitment:

- **Focus Area 1: Treatment and Prevention Strategies**
 - Milestone 1.** Assess epidemiology and mechanistic pathways of disparities in health burden of AD/ADRD.
 - Milestone 2.** Enrich the design of trials of vascular health interventions to improve their application to AD/ADRD among aging diverse populations.
- **Focus Area 2: Monitoring Changes in AD/ADRD Disparities**
 - Milestone 3.** Develop a system to monitor the magnitude and trends in health disparities in incidence of AD/ADRD.
- **Focus Area 3: Assessment**
 - Milestone 4.** Improve tools for assessment of disparities in risks, preclinical disease characteristics, and costs of AD/ADRD among health disparities populations by leveraging existing data and cohorts, designing targeted studies, and using advanced psychometric analyses for improving tools for assessment of disparities in risks, preclinical disease characteristics, and costs of AD/ADRD among health disparities populations.
 - Milestone 5.** Increase utilization of culturally- and linguistically-appropriate assessment tools within ongoing and newly generated studies of AD/ADRD and vascular health intervention trials.
- **Focus Area 4: Community Partnerships, Recruitment, and Retention**
 - Milestone 6.** Generate an AD/ADRD Health Disparities Task Force that is specifically designed to provide guidance and expertise for community engagement, study design, recruitment and retention into sites to ensure recruitment of diverse populations into newly generated epidemiological studies and clinical trials.
 - Milestone 7.** Develop novel community engagement and outreach methods and identify existing methods to facilitate engagement, understanding and partnership with health disparities populations.

These milestones will be reviewed and revised in the Summit of 2019.

II. Strategies for Ensuring Compliance

A. Peer Review

The implementation of inclusion guidelines involves the participation of review, program, policy, and grants management staff. Inclusion is first addressed by peer review. Reviewers on NIH peer review panels are given specific [guidance](#) on reviewing inclusion on the basis of sex/gender, race, ethnicity, and age when considering clinical research applications. Reviewers evaluate applications for the appropriateness of the proposed plan for inclusion by sex/gender, race, and ethnicity. For NIH-defined Phase 3 clinical trials, enrollment goals are further assessed for plans to conduct analyses of intervention effects among sex/gender, racial, and ethnic groups. Unacceptable inclusion plans must be reflected in the priority score of the application and documented in the minutes of the review session. Initial review groups make recommendations as to the acceptability of the proposed study population with respect to the inclusion policies. If issues are raised in review, program staff notify principal investigators, 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.

B. Program Monitoring and Grants Management Oversight

Prior to an award, program officials/program directors are responsible for reviewing the inclusion information in the application and indicating whether the plans are scientifically appropriate. Program staff monitor actual enrollment progress in annual progress reports and provide consultation when necessary. 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 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. Intramural IRBs review intramural research protocols for compliance with inclusion guidelines and conduct 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 pertinent IRB. 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

Institute Program Officials/Program Directors and Scientific Review Officers attended the May 11, 2018 training, Ensuring Inclusion in NIH Clinical Research: Policies and Procedures for Grants and Contracts. Staff may access the archived training on the NIH staff intranet.

NINDS staff participates in other training activities such as the OER Core Curriculum and internal Inclusion presentations.

E. Additional NINDS tools and practices used to ensure compliance with the inclusion policy

In addition to the strategies to ensure compliance mentioned above, NINDS has several tools and practices used to ensure compliance with the NIH inclusion policy. For example, NINDS has an internal enrollment tracking system called the Recruitment Planning and Monitoring System (RPMS), which allows automated data collection directly from the trial data system and real-time auditing of enrollment data. This system allows NINDS staff to customize reports, track enrollment by gender, race, and ethnicity and to compare planned and actual enrollment to identify low enrollment of minorities in real time. Poor recruitment and retention of minority populations in clinical research continues to be a significant barrier to the reduction of health disparities, although there are a few best-practice guidelines that have systematically outlined successful strategies to promote and sustain successful recruitment and retention

of minority populations. Researcher-identified best practices include using standardized project management procedures and protocols (e.g., realistic budgeting to support challenges in recruitment, such as travel/ parking reimbursement for participants), research staff cultural competency and communication training, and developing and fostering community partnerships that guide the research process. These strategies may provide mechanisms to improve retention of underrepresented groups, including women, in clinical research studies and trials¹⁹.

Additionally, NINDS also 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 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.

F. Special Focus to Inclusion, Recruitment and Retention:

[NIH AD/ADRD Recruitment & Retention Strategy](#)

On October 19, 2018 the National Institute on Aging released “Together We Make the Difference: National Strategy for Recruitment and Participation in Alzheimer’s and Related Dementias Clinical Research”. NINDS has an active role as collaborator in this NIA-led initiative. The main goal of this strategy is to outline a practical, proactive way to help investigators and study sites to enroll a more diverse study participants in AD/ADRD research studies, with a focus on underrepresented minorities²⁰.

III. Analysis and Interpretation of Data

- IC Aggregate Inclusion Data Tables:
 - [Table 2-1 \(Appendix A.1, Table 1\)](#): Total Inclusion Data Records (IDRs) for NIH-Defined Extramural and Intramural Clinical Research: Please note that the IDRs are now IERs (Inclusion Enrollment records). Table 1 shows a stable number of IERs reported from 2016 to 2018. IERs with enrollment are between 518 to 565 overall, and from 491 to 530 in U.S. sites.
 - [Table 5-1-1-C \(Appendix A.4, Table 4\)](#): Enrollment for All NIH-Defined Clinical Research, by Sex/Gender, Race, and Ethnicity.

- NIH-defined Phase 3 trials:
 - [Table 5-2-4-D \(Appendix B.3, Table 7\)](#): Enrollment for NIH-Defined Extramural and Intramural Phase 3 Trials by Sex/Gender, Race, and Ethnicity.

A. Summary of the inclusion data for the required tables

The appended tables show enrollment data for fiscal years (FY) 2016 through 2018. For the 2016-2018 reporting period, NINDS is reporting inclusion enrollment for clinical research projects tracked via the Final Research Performance Progress Report (FRPR), which captures inclusion data in a structured format and was implemented on January 1, 2017. The data in this report only include protocols where both tracking was required and actual enrollment numbers have been provided. Reported numbers are cumulative over the life of the study and do not reflect enrollment per year. Human subjects research where a tracking exception has been granted or tracking is required but enrollment has not commenced, is not included in this analysis. Furthermore, studies performing a retrospective analysis (e.g., use data from a records database) or which are no longer actively recruiting subjects or collecting follow-up data are considered as using an 'existing dataset' and are not counted the inclusion enrollment numbers.

1. Extramural and Intramural Clinical Research

[Tables 1 to 4](#): In fiscal year 2016, NINDS-funded Extramural and Intramural Clinical Research involved 491 tracked domestic protocols and 27 tracked foreign protocols with a total participant enrollment of 184,748 and 17,939 persons respectively. In fiscal year 2017, there were 530 tracked domestic extramural protocols and 35 tracked foreign protocols with a total participant enrollment of 205,813 and 24,182 persons respectively. In fiscal year 2018, there were 499 tracked domestic extramural protocols and 38 tracked foreign protocols with a total participant enrollment of 172,222 and 28,335 persons respectively. The proportion of women, minorities, and Hispanics remained stable during this three-year time period, with calculated averages and ranges as follow: women (52.5%; 50.3% - 55.8%); minorities (31.6%; 29.1% - 35.4%); Hispanics (12.7%; 10.8% - 14.2%).

2. Extramural and Intramural Phase 3 Clinical Trials

[Tables 5 to 7](#): In fiscal year 2016, NINDS-funded Extramural and Intramural Phase 3 Clinical Trials involved 17 tracked domestic protocols and 7 tracked foreign protocols with a total participant enrollment of 5,462 and 705 persons respectively. In fiscal year 2017, there were 16 tracked domestic extramural protocols and 9 tracked foreign protocols with a total participant enrollment of 3,668 and 817 persons respectively. In fiscal year 2018, there were 14 tracked domestic extramural protocols and 8 tracked foreign protocols with a total participant enrollment of 2,849 and 951 persons respectively. The proportion of women, minorities, and Hispanics remained stable during this three-year time period, with calculated averages and ranges as follow: women (36.8%; 34.8% - 39.1%); minorities (37.2%; 32.6% - 41.3%); Hispanics (12.6%; 10.7% - 14.1%). The complete aggregate enrollment data for NINDS NINDS-funded Extramural and Intramural Phase 3 Clinical Trials between fiscal years 2016-2018 are presented in Appendices 5-7 (Tables 5-7).

B. Number of NIH-defined Phase 3 clinical trials and the number that required valid analyses by sex/gender and/or race/ethnicity

From 2016 to 2018 NINDS funded 33 Phase 3 studies that required valid analysis by sex/gender and/or race/ethnicity (2016: 9 studies, 2017: 12 studies and 2018: 12 studies).

C. Link to the RCDC category reports

The RCDC report for NINDS can be accessed at the following link:

<https://report.nih.gov/RISR/#/home?ic=NINDS>

D. Notable changes to reported inclusion enrollment

It should be noted that between 2017 and 2018 the reported number of enrolled participants decreased by approximately 33,000 individuals and the reported number of enrolled African American participants decreased by approximately 10,000 individuals. This is due to the fact that for 2018 the Etiology of Geographic and Racial Differences in Stroke (REGARDS), which had previously reported enrolling 30,329 individuals (12,541 African Americans), was marked as using an existing dataset and therefore not counted in the 2018 inclusion enrollment counts. The complete aggregate enrollment data for NINDS NINDS-funded Extramural and Intramural Clinical Research between fiscal years 2016-2018 are presented in [Appendix A](#).

IV. Additional information

A. Include policy changes related to the 21st Century Cures Act.

The 21st Century Cures Act, enacted December 13, 2016, included several new requirements related to inclusion of participants in clinical research. As a result, NIH updated its policy on the Inclusion of Women and Minorities as Subjects in Clinical Research on November 28, 2017, to require studies that are both NIH-defined Phase 3 clinical trials and applicable clinical trials to report the results of analyses by sex/gender and/or race/ethnicity to ClinicalTrials.gov. This requirement is effective for competing grant awards on or after December 13, 2017, as well as contract solicitations and intramural studies initiated after this date. Additionally, NIH revised its Inclusion of Children Policy on December 19, 2017. The revised policy, now called the NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects, applies to individuals of all ages and requires reporting of participant age at enrollment in annual progress reports. The policy is effective for applications submitted on or after January 25, 2019, and contract solicitations and intramural studies initiated after this date. The 21st Century Cures Act amended the frequency of the Report of the NIH Director on the inclusion of women and minorities from biennial to triennial. Thus, this first triennial report provides information on inclusion of participants in NIH clinical research from FY 2016 – 2018. Section IV of the [Report of the Advisory Committee on Research on Women’s Health](#) includes IC reports on monitoring adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research for FY 2015 and 2016.

B. Bibliography of projects or publications with analysis(es) on sex/gender, race, and ethnicity

The following are publications with analysis on sex/gender that have not already been mentioned in previous sections and the references of this report.

U54NS048843-15: Paul D. Wellstone Muscular Dystrophy Cooperative Research Center

1. Auerbach DS, McNitt S, Gross RA, Zareba W, Dirksen RT, Moss AJ. Genetic biomarkers for the risk of seizures in long qt syndrome. *Neurology*. 2016;87:1660-1668

U54NS065712-11: The Inherited Neuropathy Consortium (INC) RDCRC

1. Jerath NU, Gutmann L, Reddy CG, Shy ME. Charcot-Marie-Tooth disease type 1x in women: Electrodiagnostic findings. *Muscle Nerve*. 2016;54:728-732
2. Jerath, N. U., Mankodi, A. , Crawford, T. O., Grunseich, C. , Baloui, H. , Nnamdi-Emeratom, C. , Schindler, A. B., Heiman-Patterson, T. , Chrast, R. and Shy, M. E. (2018), Charcot–Marie–Tooth Disease type 4C: Novel mutations, clinical presentations, and diagnostic challenges. *Muscle Nerve*, 57: 749-755. doi:10.1002/mus.25981
3. Panosyan FB, Kirk CA, Marking D, Reilly MM, Scherer SS, Shy ME, et al. Carpal tunnel syndrome in inherited neuropathies: A retrospective survey. *Muscle Nerve*. 2018;57:388-394

5R01NS058721-10: ACC: Callosal Agenesis as a Window into Common Neurodevelopmental Disorders

1. Moore CA, Staples JE, Dobyns WB, et al. Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians. *JAMA Pediatr*. 2017;171(3):288–295. doi:10.1001/jamapediatrics.2016.3982

R01NS040807-13: Family Study of Carotid Atherosclerosis and Stroke Risk

1. Beecham A, Dong C, Wright CB, Dueker N, Brickman AM, Wang L, et al. Genome-wide scan in Hispanics highlights candidate loci for brain white matter hyperintensities. *Neurol Genet*. 2017;3:e185
2. Dueker ND, Beecham A, Wang L, Blanton SH, Guo S, Rundek T, et al. Rare variants in nod1 associated with carotid bifurcation intima-media thickness in Dominican republic families. *PLoS One*. 2016;11:e0167202
3. Dueker ND, Della-Morte D, Rundek T, Sacco RL, Blanton SH. Sickle cell trait and renal function in hispanics in the united states: The northern manhattan study. *Ethn Dis*. 2017;27:11-14
4. Dueker ND, Guo S, Beecham A, Wang L, Blanton SH, Di Tullio MR, et al. Sequencing of linkage region on chromosome 12p11 identifies pkp2 as a candidate gene for left ventricular mass in Dominican families. *G3 (Bethesda)*. 2018;8:659-668

R01NS026799-28: GENE LINKAGE STUDY OF MULTIPLE SCLEROSIS SIBLING PAIRS

1. Bove R, Chitnis T, Cree BA, Tintore M, Naegelin Y, Uitdehaag BM, et al. Summit (serially unified multicenter multiple sclerosis investigation): Creating a repository of deeply phenotyped contemporary multiple sclerosis cohorts. *Mult Scler*. 2018;24:1485-1498
2. Isobe N, Keshavan A, Gourraud PA, Zhu AH, Datta E, Schlaeger R, et al. Association of hla genetic risk burden with disease phenotypes in multiple sclerosis. *JAMA Neurol*. 2016;73:795-802
3. University of California SFMSET, Cree BA, Gourraud PA, Oksenberg JR, Bevan C, Crabtree-Hartman E, et al. Long-term evolution of multiple sclerosis disability in the treatment era. *Ann Neurol*. 2016;80:499-510

P50NS053488-10: Parkinson's Disease and Dementia

1. Akhtar RS, Licata JP, Luk KC, Shaw LM, Trojanowski JQ, Lee VM. Measurements of auto-antibodies to alpha-synuclein in the serum and cerebral spinal fluids of patients with parkinson's disease. *J Neurochem*. 2018;145:489-503
2. Fleisher JE, Shah K, Fitts W, Dahodwala NA. Associations and implications of low health literacy in parkinson's disease. *Mov Disord Clin Pract*. 2016;3:250-256
3. Tao Y, Peters ME, Drye LT, Devanand DP, Mintzer JE, Pollock BG, et al. Sex differences in the neuropsychiatric symptoms of patients with alzheimer's disease. *Am J Alzheimers Dis Other Demen*. 2018;33:450-457

R01NS082296-04: Genetics and Biology of CIZ1 in Cervical Dystonia

1. Xiao J, Thompson MM, Vemula SR, LeDoux MS. Blepharospasm in a multiplex african-american pedigree. *J Neurol Sci*. 2016;362:299-303

C. Gap areas/projects specifically addressing inclusion of women and/or minority populations

Many NINDS-supported clinical trials rely on identification of eligible individuals through academic/tertiary care facilities. While this approach typically yields diverse, representative cohorts for acute disorders likely to be referred for urgent care (e.g., stroke), there are likely to be gaps in access to trials for individuals with geographic, economic, and other environmental barriers to screening and enrollment at these centers. This issue may be more prominent for prevention studies that require identification of potential participants through non-standard screening methods that may not be available equally across social and demographic strata. The NINDS-funded CREST-2 trial is attempting to address this gap directly by coordinating a community screening and referral program to reach individuals with asymptomatic carotid stenosis who are unlikely to be detected through their primary care provider. This program is still in its initial phase, so it is too early to assess its potential impact on diversity in the clinical trial cohort.

V. Appendices

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

Appendix A.1

Table 1. (Table 2-1) Total Inclusion Enrollment Records (IERs) for NIH-Defined Extramural and Intramural Clinical Research Reported Between FY2016 and FY2018

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*
2016	563	45	518	491	27	11	26	481
2017	618	53	565	530	35	12	34	519
2018	612	75	537	499	38	8	29	500

*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

Year	Sex / Gender	Total Enrollment	Total (%)	Minority	Minority (%)
2016	Female	104,041	51.3	39,843	38.3
2016	Male	92,480	45.6	30,459	32.9
2016	Unknown	6,166	3.0	1,395	22.6
2017	Female	128,442	55.8	36,212	28.2
2017	Male	95,282	41.4	29,400	30.9
2017	Unknown	6,271	2.7	1,427	22.8
2018	Female	100,782	50.3	31,634	31.4
2018	Male	90,936	45.3	26,138	28.7
2018	Unknown	8,839	4.4	3,013	34.1

Appendix A.3

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

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 (%)
2016	Female	386	0.4	4,194	4.0	20,347	19.6	161	0.2
2016	Male	325	0.4	3,782	4.1	13,322	14.4	117	0.1
2016	Unknown	4	0.1	58	0.9	1,275	20.7	1	0.0
2017	Female	342	0.3	3,947	3.1	18,046	14.0	152	0.1
2017	Male	246	0.3	3,768	4.0	12,931	13.6	128	0.1
2017	Unknown	4	0.1	60	1.0	1,295	20.7	1	0.0
2018	Female	413	0.4	3,830	3.8	11,528	11.4	119	0.1
2018	Male	360	0.4	3,391	3.7	8,072	8.9	141	0.2
2018	Unknown	2	0.0	321	3.6	2,510	28.4	1	0.0

Appendix A.3.1

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

Year	Sex / Gender	White	White (%)	More Than One Race	More Than One Race (%)	Unknown / Not Reported	Unknown / Not Reported (%)
2016	Female	62,640	60.2	7,355	7.1	8,958	8.6
2016	Male	59,067	63.9	6,805	7.4	9,062	9.8
2016	Unknown	917	14.9	3	0.0	3,908	63.4
2017	Female	89,895	70.0	6,540	5.1	9,520	7.4
2017	Male	62,404	65.5	6,207	6.5	9,598	10.1
2017	Unknown	751	12.0	1	0.0	4,159	66.3
2018	Female	66,432	65.9	7,960	7.9	10,500	10.4
2018	Male	60,753	66.8	7,455	8.2	10,764	11.8
2018	Unknown	771	8.7	3	0.0	5,231	59.2

Appendix A.4

Table 4. (Table 5-1-1-C) Enrollment for All NIH-Defined Clinical Research by Sex/Gender and Ethnicity

Year	Sex / Gender	Not Hispanic	Not Hispanic (%)	Hispanic / Latino	Hispanic / Latino (%)	Unknown / Not Reported	Unknown / Not Reported (%)
2016	Female	80,776	77.6	14,090	13.5	9,175	8.8
2016	Male	71,065	76.8	12,510	13.5	8,905	9.6

2016	Unknown	3,238	52.5	59	1.0	2,869	46.5
2017	Female	105,414	82.1	12,983	10.1	10,045	7.8
2017	Male	72,642	76.2	11,893	12.5	10,747	11.3
2017	Unknown	3,350	53.4	69	1.1	2,852	45.5
2018	Female	76,714	76.1	14,697	14.6	9,371	9.3
2018	Male	67,226	73.9	13,604	15.0	10,106	11.1
2018	Unknown	6,771	76.6	181	2.0	1,887	21.3

2. Appendix B: IC Aggregate Inclusion Data Tables, NIH-Defined Phase 3 Clinical Trials

Appendix B.1

Table 5. Enrollment for All NIH-Defined Phase 3 Clinical Trials by Sex/Gender

Year	Sex / Gender	Total Enrollment	Total (%)	Minority	Minority (%)
2016	Female	2,408	39.1	1,014	42.1
2016	Male	3,733	60.5	987	26.4
2016	Unknown	26	0.4	8	30.8
2017	Female	1,642	36.6	797	48.5
2017	Male	2,831	63.1	1,049	37.1
2017	Unknown	12	0.3	6	50.0
2018	Female	1,322	34.8	585	44.3
2018	Male	2,467	64.9	847	34.3
2018	Unknown	11	0.3	6	54.5

Appendix B.2

Table 6. Enrollment for All NIH-Defined Phase 3 Clinical Trials by Sex/Gender and Race

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 (%)
2016	Female	9	0.4	44	1.8	616	25.6	12	0.5
2016	Male	19	0.5	92	2.5	462	12.4	5	0.1
2016	Unknown	0	0.0	0	0.0	1	3.8	0	0.0
2017	Female	10	0.6	57	3.5	508	31.0	13	0.8
2017	Male	10	0.4	92	3.2	538	19.0	11	0.4
2017	Unknown	0	0.0	0	0.0	0	0.0	0	0.0
2018	Female	4	0.3	37	2.8	417	31.5	4	0.3
2018	Male	12	0.5	65	2.6	485	19.7	7	0.3
2018	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 Phase 3 Clinical Trials by Sex/Gender and Race

Year	Sex / Gender	White	White (%)	More Than One Race	More Than One Race (%)	Unknown / Not Reported	Unknown / Not Reported (%)
2016	Female	1,555	64.6	93	3.9	79	3.3
2016	Male	2,958	79.2	59	1.6	138	3.7
2016	Unknown	2	7.7	0	0.0	23	88.5
2017	Female	997	60.7	4	0.2	53	3.2
2017	Male	2,033	71.8	31	1.1	116	4.1
2017	Unknown	0	0.0	0	0.0	12	100.0
2018	Female	786	59.5	14	1.1	60	4.5
2018	Male	1,748	70.9	27	1.1	123	5.0
2018	Unknown	0	0.0	0	0.0	11	100.0

Appendix B.3

Table 7. (Table 5-2-4-D) Enrollment for All NIH-Defined Phase 3 Clinical Trials by Sex/Gender and Ethnicity

Year	Sex / Gender	Not Hispanic	Not Hispanic (%)	Hispanic / Latino	Hispanic / Latino (%)	Unknown / Not Reported	Unknown / Not Reported (%)
2016	Female	2,023	84.0	361	15.0	24	1.0
2016	Male	3,257	87.2	430	11.5	46	1.2
2016	Unknown	19	73.1	7	26.9	0	0.0
2017	Female	1,378	83.9	222	13.5	42	2.6
2017	Male	2,369	83.7	406	14.3	56	2.0
2017	Unknown	1	8.3	6	50.0	5	41.7
2018	Female	1,162	87.9	119	9.0	41	3.1
2018	Male	2,126	86.2	281	11.4	60	2.4
2018	Unknown	0	0.0	6	54.5	5	45.5

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