# 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 of the NIAMS

The mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases is to support research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; the training of basic and clinical scientists to carry out this research; and the dissemination of information on research progress in these diseases. The Institute's research portfolio includes five core mission areas: Bone Biology and Diseases, Joint Biology and Diseases and Orthopaedics, Muscle Biology and Diseases, Skin Biology and Diseases, and Systemic Rheumatic and Autoimmune Diseases. Some conditions within the NIAMS mission are very common, while some are rare — affecting only a few thousand people worldwide. The 2010 Global Burden of Disease data[1] has yielded numerous publications regarding the extent to which many conditions within the NIAMS mission affect society. For example, the 30 leading causes of disability in the United States, as measured in years lived with disability (YLDs), include low back pain, other musculoskeletal disorders, osteoarthritis, rheumatoid arthritis, and eczema (ranked as numbers 1, 3, 9, 23, and 25).[2] The high ranking of "other musculoskeletal disorders" casts light on the significant burden on society from diseases covered by the NIAMS mission. As noted in another Global Burden of Disease publication, "other musculoskeletal disorders" include relatively common disorders such as ankylosing spondylitis, carpal tunnel syndrome, fibromyalgia, psoriatic arthritis, scoliosis, and systemic lupus erythematosus, as well as rare diseases such as the autoinflammatory condition Bechet's disease.[3]

### B. Description of the NIAMS Clinical Research Portfolio

In support of its research goals and objectives, the NIAMS supports an extensive portfolio of clinical research, which includes interventional studies (i.e., clinical trials) and observational studies varying in size and complexity.

[1] Murray CJ, et al. Lancet. 2012. PMID: 23245608
[2] US Burden of Disease Collaborators. JAMA. 2013. PMID: 23842577
[3] Smith E, et al. Ann Rheum Dis. 2014. PMID: 24590181

Most of the diseases covered by the NIAMS mission areas are chronic, and many cause life-long pain, disability, or disfigurement. They affect people of all ages, racial and ethnic populations, and economic groups. Many affect women and minorities disproportionately — both in increased numbers and increased disease severity. For example, women with systemic lupus erythematosus (SLE) outnumber men nine to one. African American women are three times as likely to have SLE as are white women, and the disease is also more common in Hispanic, Asian, and American Indian women. SLE risk genes have been identified on the X chromosome, which provides potential evidence for this autoimmune disease's sex bias. Rheumatoid arthritis, osteoporosis, and osteoarthritis (in people over 45 years of age) are also more prevalent among women, whereas certain forms of ankylosing spondylitis (inflammation of the joints in the spine) occur more frequently in men.

Given what is known about the populations affected by NIAMS diseases, it is important to ensure that the funded science is appropriately including individuals of diverse racial and ethnic groups. The NIH and NIAMS are committed to the inclusion of women and minorities in all NIH-funded clinical research. This is demonstrated through the implementation of The National Institutes of Health (NIH) Revitalization Act of 1993 (Public Law 103-43) which mandates that women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, including clinical trials. Additionally, NIH-defined Phase III clinical trials must be carried out in a manner sufficient to analyze data by sex/gender and/or race/ethnicity and report these results in accordance with policy. The overall goal of the NIH Inclusion Policy is to ensure that individuals are included in clinical research in a manner that is appropriate to the scientific question under study and the prevalence of the specific disease/condition in the population/subpopulation.

## II. Strategies for Ensuring Compliance – Extramural Research

Strategies for ensuring compliance with the inclusion policy begins well before grant applications are received for review. In the funding opportunity announcement (FOA), specific language is included to support the inclusion of diverse populations in clinical studies. Any exclusion of a specific race/ethnicity or sex/gender must be scientifically justified. NIAMS scientific review, program, and grants management staff are aware of the NIH policies on inclusion on the basis of sex/gender, race, ethnicity, and age in clinical research. The NIAMS inclusion representative serves as a resource to answer questions about policy and compliance.

### A. Peer Review

The implementation of inclusion guidelines involves the participation of NIAMS review, program, clinical research management, and grants management staff. Inclusion is first addressed during the peer review process. 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 III clinical trials, enrollment goals are further assessed for plans to conduct analyses of intervention effects among sex/gender, racial, and ethnic groups. Initial review groups make recommendations as to the acceptability of the proposed study population with respect to the inclusion policies. Unacceptable inclusion plans must be reflected in the priority score of the application and documented in the minutes of the review session. Applications with unacceptable inclusion plans receive a bar to funding; an award is not issued until an acceptable resolution is received.

B. Before Award

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. NIAMS program officials discuss issues of non-compliance with applicants and advise them on how to resolve problems. The applicant then modifies the project or provides additional information to address reviewer concerns. These procedures ensure that NIAMS funds no applications with unacceptable inclusion of women and minorities.

B. Program Monitoring and Grants Management Oversight

Program staff monitor enrollment in annual progress reports and provide consultation to investigators, when necessary. 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.

For NIH-defined Phase III clinical trials, program staff monitor the requirement for sex/gender and race/ethnicity analyses in annual progress reports.

D. NIAMS Specific Procedures

Additionally, some NIAMS clinical research studies, specifically clinical trials have an additional level of oversight implemented through a Data and Safety Monitoring Board (DSMB) or a NIAMS-appointed Safety Officer (SO) who will pay special attention to the sex/gender and race/ethnicity breakdowns being reported. Often when a study is falling behind on minority recruitment, the monitoring body will request a plan from the Principal Investigator (PI) to improve the study's reach. The NIAMS and the monitoring body also pay careful attention to PI

requests to add or replace clinical study sites to ensure that a new recruitment site will contribute the right patient population in order to reach the study's inclusion targets. PIs must provide the following information before additional sites will be approved:

- Description of the patient population pool/catchment area of the new site (3-4 sentences)
- Overall Study target enrollment
- Target enrollment for new site
- Description of the expected minority population pool of the new site
- Target minority enrollment for new site

## III. Strategies for Ensuring Compliance – Intramural Research

NIAMS requires all intramural investigators conducting clinical research to provide plans for the appropriate inclusion of women and minorities, or a justification whenever representation is limited or absent, as part of their NIH protocol reviews. Intramural IRBs review the research protocols for compliance with inclusion guidelines and conduct annual Continuing Reviews. With each annual review and renewal, the investigator documents the number, sex, and race and ethnicity of participants 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 coordinates annual reporting of participant demographic data to the Office of Extramural Research (OER) and the Office of Research on Women's Health.

In 2017, a quadrennial review policy was implemented in the Clinical Center. This is a new policy for scientific review of clinical protocols which are open for four years or more. These reviews provide opportunities for the Institute Clinical Director and the PIs to discuss the adequacy of enrollment goals any issues related to meeting them. Additionally, the NIAMS Clinical Director and Clinical Operations Manager meet yearly with individual PIs to carefully review study progress regarding target enrollment.

## IV. IC training approaches

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

NIAMS Clinical Research Management staff followed this training by working individually with program and grants management staff to answer questions about changes to inclusion reporting

via the new Human Subjects System. Common issues across NIAMS were tracked and addressed at a monthly Clinical Trial Crosscutting Group meeting, attended by NIAMS program, review, and grants management staff.

On October 8, 2018, the NIAMS invited OER staff, Dawn Corbett and Rebecca Poku, to provide training on the Human Subjects System and updates to the inclusion policy reporting processes. This training was attended by program, review and grants management staff across the Institute. Minutes from this training were provided to staff that were unable to be present.

The NIAMS Inclusion Operating Procedures Working Group (IOPW) representative for NIAMS attends monthly IOPW meetings and reports updates on inclusion processes from this meeting via email or at the monthly NIAMS Clinical Trial Crosscutting Group meetings.

## V. Analysis and Interpretation of Data

### A. NIAMS Aggregate Inclusion Data Tables

NIAMS inclusion data are provided in the appendices to this report.

Inclusion data reported by clinical research studies are contained within inclusion enrollment records (IERs) within the NIH Human Subjects System. A study may have one or more inclusion enrollment records representing different study populations, depending upon how the record for a project is setup for reporting inclusion.

Table 2-1 (see Appendix 1) shows the number of IERs for NIH-Defined Extramural and Intramural clinical research projects that reported inclusion data between FY2016 and FY2018. The majority of records were from grants conducting research at U.S. sites. IERs without enrollment indicate studies that have not recruited any participants. Female only or male only IERs indicate studies that were scientifically justified to recruit only a single sex. Overall, the total number of records reporting inclusion data increased slightly each year, with an approximately 40% increase in records reporting data between 2016 (214 IERs) and 2018 (300 IERs).

### B. NIH-Defined Phase III Trials for NIAMS

As shown in Table 2-2 (see Appendix 2), the NIAMS did not have any ongoing Phase III trials to report inclusion data for in 2016. In 2017, only 1 IER reported data and it was for a study supported through the NIAMS Intramural Program, which was terminated and no longer reported data in 2018. In 2018, 2 IERs are displayed in the table as NIH-defined Phase III records; however, a closer review of these two records indicated that they were erroneously

marked as Phase III. Thus, no Phase III studies were ongoing in 2018 that required inclusion reporting.

C. NIAMS Total Enrollment for all NIH-Defined Clinical Research

The total enrollment for all NIH-Defined Clinical Research, by Sex/Gender, Race, and Ethnicity is displayed in Table 5-1-1-C (see Appendix 3). The NIAMS total enrollment counts for females and males in 2016 (64,401) and 2018 (45,632) show a decline in the number of participants enrolled. Although more IERs reported data in 2018 compared to 2016, this decline in the number of participants may be attributed to a large number of records (51) in 2018 that had not yet begun enrolling participants. It may also be related to more records with smaller cohorts enrolled. It was also noted that the percentage of females (60.8) enrolled in clinical research in 2018 was almost twice that of males (34.2). The larger number of females enrolled is not surprising given the prevalence of many NIAMS diseases affecting women disproportionately.

Of note are the data from 2017 which show a very large number (560,233) of male and female participants enrolled. Upon further review of these data reported for 2017, a large study conducting secondary analyses of existing data in the Intramural program was erroneously reported as a prospective study. Thus, the 2017 data include 500,000 participants (250,000 males and 250,000 females) that should have been excluded from reporting. With the exception of 2017 data, the percentage of minorities enrolled has stayed in the 25-30% range from 2016 to 2018. The participation of Hispanic populations has overall been steady, between 6-8% between 2016 and 2018, with comparable number of male and female participants each year.

D. Research, Condition, and Disease Category (RCDC)

As of January 2019, data on the sex/gender, race and ethnicity of participants in NIAMS clinical research by research, condition, and disease category is available on the NIH RePORT website at https://report.nih.gov/RISR/

## VI. Additional information

A. 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 III 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.

Appendix 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 | 214 | 23 | 191 | 188 | 3 | 24 | 10 | 157 |
| 2017 | 249 | 39 | 210 | 205 | 5 | 31 | 10 | 169 |
| 2018 | 300 | 51 | 249 | 244 | 5 | 32 | 9 | 208 |

*Inclusion Data Records (IERs) excluding male-only and female-only include unknown sex/gender, and combination of unknown and any sex/gender(s).

Appendix 2

Table 2-2. Total Inclusion Enrollment Records (IERs) for NIH-Defined Extramural and Intramural Phase III Trials 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 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2017 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 |
| 2018 | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 1 |

*Inclusion Data Records (IERs) excluding male-only and female-only include unknown sex/gender, and combination of unknown and any sex/gender(s).
The data presented in this report show only inclusion data records labeled as prospective data. Inclusion data records labeled as existing data are excluded.

Appendix 3

Table 5-1-1-C. Enrollment for All NIH-Defined Clinical Research, Sex/Gender by Race and Ethnicity

| Year | Sex Gender | Minority | % Minority | Total Enrollment | % Total | Not Hispanic | % Not Hispanic | Hispanic Latino | % Hispanic Latino | Unknown Not Reported | % Unknown Not Reported |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2016 | Female | 9,128 | 24.4 | 37,469 | 57.0 | 33,079 | 88.3 | 2,236 | 6.0 | 2,154 | 5.7 |
| 2016 | Male | 6,494 | 24.4 | 26,632 | 40.5 | 23,602 | 88.6 | 1,617 | 6.1 | 1,413 | 5.3 |
| 2016 | Unknown | 560 | 33.8 | 1,658 | 2.5 | 128 | 7.7 | 545 | 32.9 | 985 | 59.4 |
| 2017 | Female | 56,502 | 19.7 | 286,463 | 51.0 | 267,519 | 93.4 | 17,196 | 6.0 | 1,748 | 0.6 |
| 2017 | Male | 52,747 | 19.3 | 273,770 | 48.7 | 256,566 | 93.7 | 16,156 | 5.9 | 1,048 | 0.4 |
| 2017 | Unknown | 548 | 36.6 | 1,498 | 0.3 | 100 | 6.7 | 542 | 36.2 | 856 | 57.1 |
| 2018 | Female | 9,786 | 33.5 | 29,196 | 60.8 | 25,524 | 87.4 | 2,442 | 8.4 | 1,230 | 4.2 |
| 2018 | Male | 4,933 | 30.0 | 16,436 | 34.2 | 14,612 | 88.9 | 1,057 | 6.4 | 767 | 4.7 |
| 2018 | Unknown | 507 | 21.1 | 2,404 | 5.0 | 67 | 2.8 | 505 | 21.0 | 1,832 | 76.2 |

| 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 | White | % White | More Than One Race | % More Than One Race | Unknown Not Reported | % Unknown Not Reported |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2016 | Female | 218 | 0.6 | 1,181 | 3.2 | 4,951 | 13.2 | 45 | 0.1 | 27,294 | 72.8 | 790 | 2.1 | 2,990 | 8.0 |
| 2016 | Male | 135 | 0.5 | 1,297 | 4.9 | 3,158 | 11.9 | 36 | 0.1 | 19,363 | 72.7 | 583 | 2.2 | 2,060 | 7.7 |
| 2016 | Unknown | 0 | 0.0 | 6 | 0.4 | 9 | 0.5 | 0 | 0.0 | 130 | 7.8 | 0 | 0.0 | 1,513 | 91.3 |
| 2017 | Female | 1,247 | 0.4 | 9,269 | 3.2 | 27,193 | 9.5 | 59 | 0.0 | 244,454 | 85.3 | 1,764 | 0.6 | 2,477 | 0.9 |
| 2017 | Male | 1,110 | 0.4 | 9,471 | 3.5 | 24,776 | 9.0 | 36 | 0.0 | 235,632 | 86.1 | 1,304 | 0.5 | 1,441 | 0.5 |
| 2017 | Unknown | 0 | 0.0 | 5 | 0.3 | 1 | 0.1 | 0 | 0.0 | 73 | 4.9 | 0 | 0.0 | 1,419 | 94.7 |
| 2018 | Female | 196 | 0.7 | 1,206 | 4.1 | 5,513 | 18.9 | 28 | 0.1 | 19,635 | 67.3 | 635 | 2.2 | 1,983 | 6.8 |
| 2018 | Male | 74 | 0.5 | 1,019 | 6.2 | 2,710 | 16.5 | 11 | 0.1 | 11,373 | 69.2 | 133 | 0.8 | 1,116 | 6.8 |
| 2018 | Unknown | 1 | 0.0 | 1 | 0.0 | 1 | 0.0 | 0 | 0.0 | 12 | 0.5 | 0 | 0.0 | 2,389 | 99.4 |

The data presented in this report show only inclusion data records labeled as prospective data. Inclusion data records labeled as existing data are excluded.