The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
2015 Biennial Report Certifying Compliance
with the
National Institutes of Health (NIH) Inclusion Guidelines

I. Background/Overview

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: Arthritis and Rheumatic Diseases, Skin Biology and Diseases, Bone Biology and Diseases, Muscle Biology and Diseases, and Musculoskeletal Biology and Diseases. NIAMS supports research and research training at a variety of levels, ranging from preclinical research with model systems to translational studies to clinical and epidemiological research.

The NIAMS research portfolio covers a range of disorders. 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, eczema, and osteoporosis/inadequate fracture repair (ranked as numbers 1, 3, 9, 23, 25, and not listed, respectively).[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 the Global Burden of Disease publication, "other musculoskeletal disorders" include relatively common disorders, such as ankylosing spondylitis, fibromyalgia, psoriatic arthritis, scleroderma, and systemic lupus erythematosus, as well as rare diseases, such as the autoinflammatory condition Bechet's disease, various forms of juvenile arthritis, the inflammatory muscle disease polymyositis, rare systemic connective tissue disorders such as Ehlers-Danlos syndrome and Marfan syndrome, and different types of vasculitis (e.g., polyarteritis and Wegener's granulomatosis).[3]

Most of the diseases covered by the NIAMS mission areas are chronic, and many cause life-long pain, disability, or disfigurement. They affect millions of Americans; cause tremendous human suffering; and cost the U.S. economy billions of dollars in health care costs and lost productivity. These conditions 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

[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

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 examine differences in effects on females and males, as well as individuals of diverse racial and ethnic groups. The overall goal of the NIH 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.

The NIH defines clinical research as research with human subjects that is:

> (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.
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> (2) Epidemiologic and behavioral studies.
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> (3) Outcomes research and health services research.
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> Note: Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.[4]

It is also important to outline the definition of an NIH-defined Phase III clinical trial for the purposes of complying with the inclusion guidelines. NIH defines a Phase III trial as a broadly based clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such an investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

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[4] Exemption 4, as it pertains to research involving human subjects: defined in 46.101(b) – in order for proposed research to be exempt from the requirement of continuing IRB review and approval under Exemption 4, investigators must propose the use of data or samples that are either: existing and publicly available; OR existing and unidentifiable to the research team.

There are many research protocols that involve human subjects, but are not considered clinical research according to the NIH definition. An example of this includes research using samples collected from humans (e.g., cells, blood, urine, tissues, organs) that cannot be linked to identifiable private data or information about the living individual from whom the material was obtained. Some clinical studies with human subjects may meet the requirement for exemption from reporting. For example, a clinical study utilizing a cohort previously reported under a different study would be exempt. Also, studies with small sample sizes (i.e., less than 10), or those conducting analyses using secondary data sources do not require tracking.

The last update to the guidelines for the inclusion of women and minorities in clinical research was in October 2001. The amended guidelines and the definition noted above may be viewed at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

This report presents NIAMS' activities related to fulfilling its responsibilities under the NIH Revitalization Act of 1993, which requires the Advisory Council of each NIH Institute and Center (IC) to prepare a biennial report describing the manner in which the IC has complied with the Act. It includes a summary of the Extramural Program (EP) inclusion data for Fiscal Years (FY) 2013 and 2014. The report also highlights training and education efforts implemented by NIAMS for EP staff and investigators, as well as strategies for ensuring policy compliance.

II. Strategies for Ensuring Policy Compliance with Inclusion Guidelines

A. NIAMS Procedures for Ensuring Compliance

Compliance and implementation of the inclusion guidelines relies on the Review, Program, and Grants Management staff, as well as the Clinical Coordinators. Each of these areas has a specific function to ensure correct implementation of the guidelines.

Inclusion is first addressed with the review of applications, facilitated by the Scientific Review Officer (SRO). The SRO evaluates applications to ensure that the required information regarding gender and minority enrollment in the study is included along with information demonstrating how the investigator plans to meet these recruitment goals. The Initial Review Group (IRG) makes recommendations as to the acceptability of the proposed study population with respect to the inclusion policy. Applications with insufficient inclusion plans receive an unacceptable gender or minority code, resulting in a bar-to-funding. Such clinical research studies cannot be funded until the NIAMS Program and Grants Management staff members are assured of compliance from the investigators and a revision to the inclusion plan is complete. The Clinical Coordinators ensure that the applicable target and inclusion data are entered into the NIH tracking system known as the Population Tracking database.

Annual inclusion reports are carefully reviewed against projected enrollment targets to ensure that adequate progress is being made. Investigators are notified if there are discrepancies related to either the data provided or their progress toward the target. When appropriate, NIAMS' Program staff provides consultation to improve enrollment of women and minorities.

B. Staff Training on the Utilization of the Tracking System

NIAMS has taken the following steps to ensure that the Scientific Review, Program, Grants Management, and the Clinical Coordinators are properly trained to monitor and document women and minority inclusion requirements.

- The Clinical Coordinators encourage all new and existing NIAMS staff involved with clinical research to take the online training, "Inclusion of Women and Minorities in Clinical Research."

- NIAMS invites staff from the Office of Extramural Programs to give a presentation and updates on human subjects protection on an annual basis.

- Scientific Review staff ensure the dissemination and interpretation of inclusion policy requirements to all grant application reviewers.

- NIAMS' Clinical Coordinators work regularly with Program and Grants Management staff on issues related to tracking requirements and assignment of tracking codes. They provide training to NIAMS' EP Divisions on requirements for human subjects tracking and continue to be a resource for NIAMS' EP staff.

- A Standard Operating Procedure was developed to document the policies and procedures related to retrieving, entering, and monitoring population tracking data for NIAMS grants, contracts, and cooperative agreements.

- The Clinical Trials Crosscutting Group (CTCG), an internal NIAMS group, uses its monthly meetings as a forum for discussion of clinical trials and questions related to tracking and inclusion issues. This meeting, Co-Chaired by the NIAMS Clinical Coordinators, has been used to disseminate new information related to the policies and procedures for inclusion and any other human subjects related matters.

III. Analysis and Interpretation of Data

The review of NIAMS aggregate data for FY 2013-2014 shows that women and minorities continue to be well-represented in NIAMS-supported extramural clinical research studies. The total number of participants enrolled in clinical research since the last biennial report presented in 2013 has not changed significantly, from 86,837 total participants in FY 2011-2012, compared to 87,461 total participants in FY 2013-2014. The FY 2013-2104 data represents enrollment from 267 clinical research studies. Data in 2014 show a 14 percent increase in White participation (83.2 percent) over 2013 (69.0 percent), which has resulted in a lower combined minority percentage in 2014 (11.6 percent) compared to 2013 (22.7 percent). These fluctuations could be explained by an increase in studies that began recruitment in FY 2014 with higher percentages of White participants, and also an increase in the number of studies funded in less diverse areas.

FY 2013 Inclusion Data

In FY 2013, 137 clinical research studies reported enrolling 40,143 human subjects. An additional 54 "early-stage" clinical studies that had been entered into the data system had not yet begun enrollment and, therefore, inclusion data were not available. Table 1 shows the rates of participation by gender, race, and ethnicity. Female participation (55.3 percent) remains

higher than male participation (44.1 percent), similar to what was observed in the last biennial report. This is likely attributable to many of the diseases within the NIAMS mission that disproportionately affect women (e.g., osteoporosis, fibromyalgia, rheumatoid arthritis). The percentage of Black participants has decreased by half since the last report, from 21.8 percent to 10.6 percent. There have also been slight decreases in the numbers of Asian, American Indian/Alaskan Native, and Hawaiian/Pacific Islander participants. These decreases may indicate that studies with higher minority participation closed and no longer were reporting recruitment in FY 2013. NIAMS-supported studies are recruiting White participants at a rate (69.0 percent) much closer to what is observed in the U.S. population (72.4 percent), based on the 2010 U.S. Census data. The Hispanic category is an ethnic category and the data is collected separately from the race information. Data for FY 2013 show that the majority of participants in the NIAMS studies are Not Hispanic (84.1 percent), however 4.9 percent are identified as Hispanic, while 11.0 percent chose to report their ethnicity as unknown or the data could not be collected. The percentage of Hispanics in NIAMS studies is lower in comparison to the Hispanic representation in the U.S. population (16.3 percent) according to the U.S. Census data.

FY 2014 Inclusion Data

In FY 2014, 130 clinical research studies reported enrolling 47,318 human subjects. Eighty six "early-stage" clinical studies could not be included in this total since they had not yet begun enrollment. Similar to previous years, female participation (55.3 percent) continued to exceed male participation (44.2 percent). Asian and Black participation fell from 10.7 percent and 10.6 percent, respectively, in FY 2013 to 2.3 percent and 6.9 percent, respectively, in FY 2014; however White (83.2 percent) participation increased from 69.0 percent in FY 2013 to 83.2 percent in FY 2014. Some reasons for the increase are explained above. Table 2 shows the distributions by gender, race and ethnicity for FY 2014.

When compared to the total number of participants reported in the FY 2011-2012 report (87,197), there are only 264 more participants in the FY 2013-2014 report (87,461).This small increase in participants is not unusual given that no particularly large studies began recruitment in FY 2013-2014. Also, the number of studies that began reporting enrollment in FY 2013-2014 was less (267) than in FY 2011-2012 report (296); however, this did not have a significant impact in the overall number of human subjects recruited in NIAMS clinical research. Table 3 presents the number of protocols reporting inclusion data since 2009. Since the number of studies that have been tracked has been fairly consistent, it is possible that the NIAMS is supporting studies with smaller cohorts than in previous years, thus leading to a downward trend in the number of participants tracked in clinical research.

The clinical research inclusion data from FY 2013 and FY 2014 presented in this report demonstrate compliance with the NIH guidelines established in response to the NIH Revitalization Act of 1993.

Recruitment and retention of women and minority participants in clinical research continues to be a priority for NIH and NIAMS. NIAMS will continue to work internally and with our extramural investigators to ensure that all racial and ethnic groups are well-represented in NIAMS-funded clinical research.

Table 1: 2013 NIAMS Aggregate Enrollment Data

New Form: Total of All Subjects Reported Using the 1997 OMB Standards — Number of Protocols with Enrollment Data: 137

	Total of All Subjects by Race								Total of All Subjects by Ethnicities			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Not Reported	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	98	1,444	2,865	17	15,976	158	1,779	22,337	18,093	1,157	3,087	22,337
	0.44%	6.46%	12.83%	0.08%	71.52%	0.71%	7.96%	55.64%	81%	5.18%	13.82%	55.64%
Male	59	2,832	1,380	13	11,718	135	1,286	17,423	15,651	766	1,006	17,423
	0.34%	16.25%	7.92%	0.07%	67.26%	0.77%	7.38%	43.4%	89.83%	4.4%	5.77%	43.4%
Unknown	1	7	4	0	20	85	266	383	10	56	317	383
	0.26%	1.83%	1.04%	0%	5.22%	22.19%	69.45%	0.95%	2.61%	14.62%	82.77%	0.95%
Total	158	4,283	4,249	30	27,714	378	3,331	40,143	33,754	1,979	4,410	40,143
	0.39%	10.67%	10.58%	0.07%	69.04%	0.94%	8.3%	100%	84.08%	4.93%	10.99%	100%

Table 2: 2014 NIAMS Aggregate Enrollment Data

New Form: Total of All Subjects Reported Using the 1997 OMB Standards — Number of Protocols with Enrollment Data: 130

	Total of All Subjects by Race								Total of All Subjects by Ethnicities			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Not Reported	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	103	697	1,925	17	21,866	273	1,270	26,151	23,607	1,196	1,348	26,151
	0.39%	2.67%	7.36%	0.07%	83.61%	1.04%	4.86%	55.27%	90.27%	4.57%	5.15%	55.27%
Male	86	699	1,317	26	17,436	261	1,059	20,884	18,810	910	1,164	20,884
	0.41%	3.35%	6.31%	0.12%	83.49%	1.25%	5.07%	44.14%	90.07%	4.36%	5.57%	44.14%
Unknown	1	2	4	0	43	85	148	283	25	48	210	283
	0.35%	0.71%	1.41%	0%	15.19%	30.04%	52.3%	0.6%	8.83%	16.96%	74.2%	0.6%
Total	190	1,398	3,246	43	39,345	619	2,477	47,318	42,442	2,154	2,722	47,318
	0.4%	2.95%	6.86%	0.09%	83.15%	1.31%	5.23%	100%	89.7%	4.55%	5.75%	100%

Table 3: 2009-2014 Summary of Inclusion Data by Year

Year	Number of Protocols Reporting Inclusion Data	Total Number of Participants Enrolled
2009	151	79,701
2010	152	61,376
2011	146	50,240
2012	150	36,957
2013	137	40,143
2014	130	47,318