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Report to Congressional Requesters

October 2015

# NATIONAL INSTITUTES OF HEALTH

# Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research

Accessible Version

GAO-16-13

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## Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research

GAO Highlights

Highlights of GAO-16-13, a report to congressional requesters

## Why GAO Did This Study

Women make up over half the U.S. population, but historically have been underrepresented in clinical research supported by NIH and others. As a result, differences in the manifestation of certain diseases and reactions to treatment in women compared with men were not identified. For example, there have been instances of women having adverse effects that differed from those of men related to medications and other treatments. NIH's Inclusion Policy established requirements governing women's inclusion in its clinical research.

GAO was asked to provide information on women's participation in NIH research. Among other reporting objectives, GAO examined (1) women's enrollment and NIH's efforts to monitor this enrollment in NIH-funded clinical research; and (2) NIH's efforts to ensure that NIH-funded clinical trials are designed and conducted to analyze potential sex differences, when applicable. To do this, GAO reviewed relevant laws and policies, including the Inclusion Policy, and federal standards for internal control; reviewed and analyzed NIH enrollment data from fiscal years 2005-2014; and interviewed NIH and IC officials and other experts.

## What GAO Recommends

GAO recommends that NIH examine and report more detailed data on women's enrollment in NIH-funded studies, and collect, examine, and report data on the extent to which these studies include analyses of potential differences between women and men. NIH agreed with GAO's recommendations and plans to take action to implement them.

View GAO-16-13. For more information, contact Linda Kohn at (202) 512-7114 or KohnL@gao.gov.

## What GAO Found

Data from the National Institutes of Health (NIH) show that more women than men were enrolled in NIH-funded clinical research for fiscal years 2005-2014, but NIH does not make certain enrollment data readily available to interested parties or examine other detailed data to identify potential challenges to enrolling women in specific research and disease or condition areas. In fiscal year 2014, for example, NIH reported that across all of the clinical research studies it funded—including phase III clinical trials, the largest studies involving human subjects—57 percent of enrollees (16.4 million) were women. NIH collects enrollment data from individual awardees through its Institutes and Centers (IC)—which generally fund studies in different research areas—and publicly reports data on aggregate enrollment as part of its implementation of the Inclusion Policy developed to implement provisions of the NIH Revitalization Act of 1993. However, NIH does not make the IC-level enrollment data from each of the 25 ICs that report data readily available to interested parties, so that interested parties must make an effort to seek out this data. In addition, NIH does not routinely examine more detailed enrollment data, such as enrollment data organized by the disease and condition being studied. As a result, NIH is limited in its ability to identify whether women are sufficiently represented in studies in specific areas—such as cardiovascular disease—or if the agency-wide data inadvertently mask enrollment challenges. By not examining more detailed data on enrollment below the aggregate level, NIH cannot know whether it is adequately including women in all of the research it supports, in a manner consistent with its Inclusion Policy. Further, NIH's reporting and monitoring in this area is inconsistent with federal internal control standards, which call for agencies to have controls to help ensure effective information flow and effective monitoring of agency activities.

NIH requires that phase III clinical trial awardees consider whether analysis of potential differences in outcomes between women and men is needed in their studies—one of the key requirements of its Inclusion Policy; however, the agency does not maintain, analyze, or report summary data to oversee whether analysis of outcomes by sex are planned or conducted. NIH officials told GAO that they rely on peer review and program officer monitoring to ensure awardee compliance with the analysis requirement. However, NIH program officers do not have a required field in a reporting system or other means to record the information they collect to monitor awardees' analysis plans and compliance with the Inclusion Policy requirement. In addition, there is no data element in NIH's data system to indicate whether an awardee's study should or does include plans for an analysis of potential differences in research outcomes by sex. As a result, NIH lacks summary data, such as the percentage of awardees in a given year with trials designed to identify potential differences in clinical outcomes by sex. Without this summary information, NIH cannot report this information in the agency's biennial reports to Congress and other stakeholders. The lack of summary data and reporting compromises NIH's monitoring of its implementation of the Inclusion Policy and conflicts with federal internal control standards, which call for agencies to ensure the flow of information about agency activities, provide for internal and external communication, and conduct periodic monitoring. Further, it limits NIH's assurance that it is supporting research that can be used to shape improved medical practice for both women and men.

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**Abbreviations**

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| HHS | Department of Health and Human Services |
| IC | institute and center |
| IOM | Institute of Medicine |
| NCI | National Cancer Institute |
| NHLBI | National Heart, Lung, and Blood Institute |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| OER | Office of Extramural Research |
| ORWH | Office of Research on Women's Health |

U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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Congressional Requesters

The Department of Health and Human Services' (HHS) National Institutes of Health (NIH) is the nation's largest public funder of biomedical research, with a budget of more than $30 billion for fiscal year 2015. Although women make up just over half the U.S. population, their health needs have historically been underrepresented in the research supported by NIH and others.[1] This underrepresentation in clinical research has led to failures in recognizing differences between women and men in the prevalence of certain diseases, in how certain diseases manifest, and in the reactions to treatments.[2] As a result, there have been notable instances of women experiencing adverse effects and other poor outcomes that differed from those experienced by men related to health care treatments. For example, in 2013, the Food and Drug Administration lowered the recommended dose of a popular sleep drug for women after it was determined that women and men metabolize the drug differently. That difference left women with more of the drug in their bodies the next morning and therefore at a greater risk of driving while impaired. Women's health research advocates have stated that without the routine consideration of the potential for these and other clinical differences between women and men, the nation does not receive the full value of its public investment in biomedical research.

It has been over 2 decades since Congress passed the NIH Revitalization Act of 1993 (Revitalization Act), which provided statutory requirements for NIH to follow regarding research on women's health.[3] Specifically, the

[1]NIH's first policy for the inclusion of women in clinical research was established in 1986. Prior to that, little clinical research on women's health was conducted, for reasons including concerns over fetal exposure to experimental substances, the variability in women's hormonal status, and the assumption that results of research on men could be extrapolated to women.

[2]For example, research has identified differences in how certain diseases manifest themselves in women compared to men, including cardiovascular disease, lung cancer, depression, and Alzheimer's disease.

[3]Pub. L. No. 103-43, 107 Stat. 122 (June 10, 1993). The Revitalization Act also requires specific actions related to enrollment of minorities in NIH clinical research. Examination of NIH's activities regarding minority enrollment was outside the scope of our work.

Revitalization Act contained provisions for the enrollment of women in clinical research studies—including clinical trials—and requiring that clinical trials be designed and carried out to be able to provide for a valid analysis of whether the variables being studied affect women and men differently.[4] The Revitalization Act also required NIH to establish guidelines for including women in clinical research. In 2000, we examined NIH's efforts to conduct research on women's health over the previous decade. We reported that NIH had made significant progress in implementing the Revitalization Act by issuing guidelines to implement the law, conducting extensive training for scientists and reviewers, and implementing a centralized data system to monitor enrollment.[5] However, we also recommended in 2000 that NIH continue to make improvements, including better implementation of the requirement that some studies be designed to permit analysis of results by sex, which could reveal whether interventions affect women and men differently. In response, NIH developed specific guidance on this aspect of the policy for applicants and for the reviewers who evaluate applicants for NIH funding.

Partly in response to our recommendation, in October 2001, NIH amended its *Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research* (Inclusion Policy), which is in place today. The Inclusion Policy establishes two key requirements for NIH-funded researchers conducting clinical research studies. Specifically, researchers must (1) design research plans that detail the breakdown of their studies' participants by sex and provide a rationale for their planned enrollment; and (2) for certain clinical trials, include plans for analyzing

[4]NIH defines clinical research as patient-oriented research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which a researcher directly interacts with human subjects. This includes all phases of clinical trials, which are research studies in which one or more human subjects are prospectively assigned to one or more interventions (which may include a placebo or other control) to evaluate the effects of those interventions—including experimental drugs, treatments, and devices—on health-related biomedical or behavioral outcomes. In addition to clinical trials, clinical research includes epidemiological, behavioral, and observational studies.

In this report, we refer to "sex" rather than "gender" because sex is a biological variable and gender is a psychosocial construct.

[5]GAO, *Women's Health: NIH Has Increased Its Efforts to Include Women in Research*, GAO/HEHS-00-96 (Washington, D.C.: May 2, 2000).

outcomes for potential sex differences, when appropriate, as determined by prior scientific evidence.[6]

Despite these efforts, reports from the Institute of Medicine (IOM) published in 2010 and 2012 stated that continued efforts—by NIH and others—are needed to improve both the overall status of women's health research and, in particular, the ability of researchers to conduct analysis of study results by sex to determine whether outcomes differ for women compared to men.[7] While experts acknowledge that there have been increases in women's enrollment in clinical research studies since the passage of the Revitalization Act, the IOM and others have found that even when women are included in clinical trials, the results of analyses are often not reported by sex—even when the overall results are published in peer-reviewed journals. A recent study found that less than half of NIH-funded clinical trials overall had been published in a peer-reviewed biomedical journal within 30 months of trial completion, and in response, NIH officials stated that other means of sharing such results—besides publication in scientific literature—is needed.[8] Experts have stated that insufficient reporting of clinical trial results by sex limits the ability of researchers to identify potentially important sex differences that may ultimately affect patient care.

[6]NIH determined that this requirement of the Inclusion Policy is limited to phase III clinical trials, the largest clinical trials involving human subjects and the most likely to result in broad changes in public health policy and/or standards of care.

[7]Institute of Medicine, *Women's Health Research: Progress, Pitfalls, and Promise* (Washington, DC: The National Academies Press, 2010), and *Sex-specific Reporting of Scientific Research: A Workshop Summary* (Washington, DC: The National Academies Press, 2012). IOM is a component of the National Academy of Sciences, a private, nonprofit organization chartered by Congress to provide independent, objective advice on matters related to science, technology, and medicine.

[8]J. S. Ross, et al. "Publication of NIH-funded Trials Registered in ClinicalTrials.gov: Cross-sectional Analysis." *BMJ*, 344:d7292. (2012).

You asked us to provide information on women's participation in NIH-funded clinical trials, including NIH's policies regarding enrollment, and both the analysis and reporting of clinical trial results. In this report, we examine NIH's implementation of the Inclusion Policy, in particular,

1. the level of women's enrollment and NIH's efforts to monitor this enrollment in NIH-funded clinical research; and
2. NIH's efforts to ensure that NIH-funded clinical trials are designed and conducted to analyze potential sex differences, when applicable.

We also examine

3. NIH's efforts to help ensure that researchers make the results of clinical trials public, including sex-specific results, when appropriate.

In addition, Appendix I of this report summarizes information on the factors affecting women's participation in clinical research, as were most frequently cited in published literature.

To address these objectives, we reviewed relevant laws and policies and interviewed NIH officials and other relevant experts. Specifically, we reviewed laws and policies (including proposed policies)—in particular, the Revitalization Act and NIH's Inclusion Policy. We interviewed officials from NIH's Office of Research on Women's Health (ORWH), the Office of Extramural Research (OER), and the National Library of Medicine. We also interviewed representatives from selected NIH Institutes and Centers (ICs) that we identified as among the largest ICs both in terms of the total amount of award funding provided to researchers and in terms of the total number of research awards made: the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Disease (NIAID), and the National Heart, Lung, and Blood Institute (NHLBI).[9] In addition to interviewing the leadership of the selected ICs, we also interviewed program officers from the selected ICs who work directly with NIH awardees. We also interviewed officials from the Society for Women's Health Research, the Women's Health Research Institute at Northwestern University, and the editors of one major medical journal, as well as other individual researchers and experts, to gain perspectives on women's

[9]NIH is composed of 27 institutes and centers, each with its own mission; 24 of the 27 ICs receive their own appropriation from Congress.

inclusion in biomedical research supported by NIH and others and on the analysis and reporting of research outcomes.

To describe the level of women's enrollment and NIH's efforts to monitor women's enrollment in NIH-funded clinical research, we obtained and reviewed enrollment data for all NIH-funded clinical research studies across NIH and for each of the ICs. For the aggregate NIH data, we reviewed 10 years of enrollment data (fiscal years 2005-2014), and for IC-level data, we reviewed 4 years of enrollment data (fiscal years 2011-2014) for the 25 ICs that collect and report such data.[10] We also reviewed documentation of NIH's data collection tools, and interviewed NIH and IC officials—from the offices identified above—regarding their oversight of enrollment data. Through our review of the data and supporting documentation and our interviews with NIH and IC officials, we determined these enrollment data to be sufficiently reliable for our purposes. As part of our review, we examined the extent to which NIH's monitoring efforts were consistent with the standards for internal control in the federal government—specifically those related to information, communication, and monitoring.[11]

To describe NIH's efforts to ensure that NIH-funded clinical trials are designed and conducted to analyze potential sex differences, when applicable, we collected and reviewed NIH guidance and tools regarding how to assess applicants' and awardees' compliance with the analysis requirement of the Inclusion Policy, as it applies to certain clinical trials. We reviewed NIH reports and documentation related to implementation of the Inclusion Policy. We also interviewed NIH and IC officials specifically regarding their efforts to monitor implementation of the analysis requirement of the Inclusion Policy. As part of our review, we examined the extent to which NIH's efforts were consistent with the standards for

[10]IC-level enrollment data were only available for these 4 years (fiscal years 2011 through 2014), as data from fiscal year 2010 and earlier were not collected or reported in the same manner, making the data not comparable to data collected and reported in fiscal year 2011 and later. In addition, we report on enrollment for only 25 of the 27 ICs because 2 ICs, the Center for Information Technology and the Center for Scientific Review, do not conduct or fund any clinical research studies, and thus are not included in our discussion of IC enrollment.

[11]GAO, *Internal Control: Standards for Internal Control in the Federal Government*, GAO/AIMD-00-21.3.1 (Washington, D.C.: November 1999). Internal control is synonymous with management control and comprises the plans, methods, and procedures used to meet missions, goals, and objectives.

internal control in the federal government—specifically those related to control activities, information, communication, and monitoring.[12]

To describe NIH's efforts to help ensure that researchers make the results of clinical trials public, including sex-specific results when appropriate, we reviewed NIH policies and procedures regarding the reporting of clinical trial results (particularly through public venues), including proposed policies, and documentation of NIH activities related to sharing of clinical trial results. We examined the NIH registry and results website—ClinicalTrials.gov—and related materials. We also reviewed the publication policies of selected scientific journals to determine whether they addressed reporting of results by sex.[13]

We conducted this performance audit from September 2014 to October 2015 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

## Background

Headed by a presidentially appointed and Senate-confirmed director, NIH comprises 27 ICs and an Office of the Director. NIH's ICs both conduct and support biomedical research specific to their unique missions, which generally focus on a specific disease, a particular organ, or a stage in life (e.g., childhood). Each of the ICs has its own director and staff, as well as its own advisory council or board, which helps to support and oversee the IC's work. Within the Office of the Director are offices responsible for issues, programs, and activities that span NIH components, particularly research initiatives and issues involving multiple ICs.

### NIH-Supported Research and Clinical Trials

NIH's biomedical research that focuses on humans—its clinical research studies—includes clinical trials of biomedical or behavioral interventions such as new drugs, medical treatments, and surgical procedures and

[12]GAO/AIMD-00-21.3.1.

[13]These publications included *JAMA*, *The Lancet*, *Nature*, *Surgery*, and other peer-reviewed journals identified by Stanford University's Gendered Innovations project.

devices.[14] Clinical trials are divided into four phases. In phase I clinical trials, which typically include 20 to 80 people, researchers test a new biomedical or behavioral intervention on human subjects for the first time to evaluate safety. In phase II clinical trials, the intervention is given to a larger group of people, 100 to 300 participants, to further evaluate efficacy and safety. In phase III clinical trials, the intervention is given to even larger groups—from several hundred to several thousand participants—to compare the intervention to commonly used or experimental interventions.[15] Finally, phase IV studies are conducted after the intervention has been marketed, in order to gather information on long-term use.

NIH's ICs support clinical trials predominantly through "extramural research"—awarding funds to researchers at universities or other research entities (awardees) through grants, contracts, and cooperative agreements.[16] Of NIH's 27 ICs, almost all fund extramural research projects. These ICs use a standard peer review process to inform the final decisions on which extramural research projects to fund.[17] The size and composition of the ICs' clinical trial portfolios vary substantially,

[14]NIH's clinical research on human subjects is considered applied research. NIH funds both applied research and basic research, which does not directly involve human subjects or direct testing of treatments.

[15]In this report, when we use the term "phase III clinical trials," we are referring to NIH-defined phase III clinical trials. An NIH-defined phase III clinical trial is a broadly based prospective 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 investigation is to provide evidence leading to a scientific basis for considering a change in health policy or standards of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

[16]Extramural research represents about 80 percent of NIH's budget. Intramural research, which represents about 10 percent of NIH's budget, involves research performed by NIH scientists in NIH laboratories.

[17]When reviewing applications for extramural research studies, NIH follows a process of peer review, established by law. This peer review system has two sequential levels of peer review. The first level involves panels of experts to assess the scientific merit of the proposed science. The second level involves panels of experts and leaders of non-science fields, including patient advocates, who, in addition to scientific merit, also consider the mission and strategic plan goals, public health needs, scientific opportunities, and portfolio balance of the IC funding the research. After NIH's peer review process is concluded, IC directors make extramural funding decisions.

depending on such factors as the IC's budget, mission, and the scientific goals of any given study. For example, some ICs support few if any phase III clinical trials.

In fiscal year 2014, NIH's ICs reported funding of nearly $30 billion for all biomedical research.[18] Of that amount, NIH estimates that—based on reporting categories HHS developed for use by all of its agencies—$23.9 billion (80.3 percent) funded research related to the health of both women and men, $4 billion (13.2 percent) funded research related to women's health, and an estimated $1.9 billion (6.4 percent) funded research related to men's health. (See Appendix II for more details on estimated fiscal year 2014 funding for selected diseases and conditions of particular relevance for women.) To determine these amounts, NIH annually assigns its research funding to certain women's health disease and condition categories—such as breast cancer or heart disease. Additionally, NIH classifies this funding as either related to the health of both sexes or as supporting research on women's health only or men's health only by using HHS's calculation guidelines.[19] NIH reports these funding estimates in HHS's annual congressional budget justification and in ORWH's biennial *Report of the Advisory Committee on Research on Women's Health*.[20]

## The NIH Revitalization Act of 1993 and NIH Inclusion Policy

The Revitalization Act required NIH to ensure the appropriate inclusion of women in NIH-funded clinical research, including clinical trials. The Revitalization Act contained provisions that required NIH to, among other things, ensure that women are included in all NIH-funded clinical research, and report on compliance with the inclusion provisions of the Act. Additionally, the Revitalization Act requires NIH to ensure that clinical trials are designed and carried out in a manner sufficient to allow for valid analysis of the extent to which the outcomes measured in the trial affect women differently than men. NIH subsequently determined that this

[18]Amounts reported by NIH are based on obligations and not actual expenditures.

[19]HHS's calculation guidelines are based on enrollment for trials involving human subjects. For research in which men and women are included, but enrollment information is not known, agencies are instructed to multiply spending by 50 percent to determine how much was spent on women's health and men's health, respectively.

[20]For a link to the report, visit http://orwh.od.nih.gov/about/acrwh/index.asp, which we accessed July 21, 2015.

particular requirement only applied to phase III clinical trials, as they are the largest clinical trials involving human subjects and the closest to effecting broad changes in public health policy and standards of care.

The Revitalization Act also directed NIH to develop guidelines for including women in clinical research and report biennially to Congress on NIH's compliance with this policy. The resulting Inclusion Policy, the current version of which has been in place since October 2001, requires NIH applicants conducting clinical research to

1. design research plans that detail the breakdown of their studies' participants by sex and provide a rationale for their planned enrollment for all clinical research studies; and
2. include plans for analyzing outcomes for potential sex differences for NIH-defined phase III clinical trials, when appropriate, as determined by consideration of prior scientific evidence.[21]

In addition to NIH ICs, several NIH offices play a role in implementing the Inclusion Policy, particularly ORWH, which was established in 1990—and codified in the Revitalization Act—to promote women's health research, and OER, which administers and manages NIH grants policies, operations, and data systems. Since November 2011, the implementation of NIH's Inclusion Policy has been overseen by the Subcommittee on Inclusion Governance, which comprises senior NIH officials from ORWH,

[21]Specifically, the Inclusion Policy states that researchers must consider prior studies to determine if (1) prior studies support the existence of significant sex differences in intervention effect, (2) prior studies neither support nor negate the existence of sex differences, or (3) prior studies support the existence of no significant differences. A significant difference is defined as a difference of clinical or public health importance. If prior studies either support the existence of sex differences or neither support or negate the existence of sex differences, then researchers must include in their applications plans for collecting data and conducting valid analysis to identify potential sex differences in the effect of the intervention being studied. If prior studies support no significant sex differences in intervention effect, a specific analysis is not required; however the inclusion and analysis of sex is still strongly encouraged.

OER, and several ICs.[22] This committee, co-chaired by the ORWH director and staffed by the NIH Inclusion Policy Officer from OER, is charged with examining and considering current NIH policies related to the inclusion of women in NIH-funded clinical research. In addition, the implementation of the Inclusion Policy is monitored by the Advisory Committee on Research on Women's Health (Women's Health Advisory Committee), whose creation was mandated by the Revitalization Act, as well as by the individual IC's directors and advisory councils or boards.[23]

## NIH's Extramural Awards Management Process

During the peer review process, applicants' plans for including women, as appropriate, are reviewed and assessed along with the applicants' plans to meet other requirements or considerations that are outlined in the funding opportunity announcement or research solicitation. The outcome of these assessments—scores from the peer reviewers—inform the funding decisions made by the ICs. Prior to awards being made, program officers or other IC staff may advise awardees on additional information required before an award can be released, and the resolution of any concerns raised during the peer review stage—including concerns related to adherence to the Inclusion Policy. After awards are made, NIH's awardees are responsible for managing their day-to-day activities in accordance with NIH requirements, and the IC making the award is responsible for the awarded funds and for monitoring progress and compliance with NIH policies, including the Inclusion Policy. IC program officers monitor awardees through a variety of methods—including reviews of reports and correspondence from the awardee, and site visits—to identify potential problems with scientific progress, compliance, and areas where technical assistance might be necessary. One such

[22]Prior to 2011, NIH had other means for monitoring inclusion in clinical research. The first electronic data system for monitoring inclusion was deployed in 2002. In 2009, an internal task force was formed to consider approaches for accomplishing the goals of NIH's Inclusion Policy. A specific recommendation was the restructuring of inclusion governance to align it more closely with the overall governance structure at NIH. The result is that this subcommittee is part of the overall NIH governance structure and reports to NIH's Extramural Activities Working Group. Additionally, in 2011, NIH hired an Inclusion Policy Officer to provide a centralized point of contact to coordinate policies, procedures, and reporting related to the implementation of the Inclusion Policy.

[23]Women's Health Advisory Committee members, who meet twice a year, are selected from among physicians, practitioners, scientists, and other health professionals who are not federal employees and who have a clinical practice, research specialization, or professional expertise that includes a significant focus on research relevant to women's health. Also, by law, a majority of the members of the committee shall be women.

report that program officers review is the annual progress report—which includes data on study enrollment, among other things. Awardees submit information, including enrollment data, through the Electronic Research Administration (eRA) Commons, which is part of NIH's electronic data collection and grants administration system that is used by awardees and program officers to access and share administrative information related to research awards.

## More Women Than Men Were Enrolled in NIH Research Overall, but NIH Does Not Examine Detailed Data to Identify Potential Challenges to Enrolling Women

NIH data show that over the last decade more women than men have been enrolled across all NIH-funded clinical research, including phase III clinical trials. NIH publicly reports aggregate enrollment numbers on a biennial basis; however, it does not routinely make detailed IC enrollment data readily available or examine more detailed enrollment data by disease and condition, in order to identify potential challenges to enrolling women in certain research and disease or condition areas.

### NIH Data Show More Women than Men Enrolled in NIH-Funded Clinical Research

NIH requires each awardee to report enrollment, including enrollment by sex, for each of their NIH-funded research awards, including phase III clinical trials. As of fiscal year 2015, these data are reported to NIH through its Inclusion Monitoring System—one part of NIH's awardee data system. Program officers review these data at least annually to determine whether actual enrollment is consistent with the enrollment planned in the research design.[24] The program officers use a designated checklist, among other tools, to document their monitoring as part of the annual progress report review process. According to NIH officials, awardee enrollment data are aggregated by each IC and presented in and discussed during meetings held by each IC's advisory board or council, which are open to the public. The IC-level enrollment data are certified as

[24]Program officers review the progress report and inclusion enrollment data and determine whether progress is satisfactory. If there are any concerns with progress or compliance, they may follow-up with the awardee in writing, by email, by phone, or at times, with a site visit.

being compliant with the Inclusion Policy by the IC's advisory board or council and by the IC Director and included in an IC-level enrollment report. The certified IC enrollment reports are submitted to ORWH and OER, where, according to NIH officials, the data are checked for consistency and errors as part of a quality control process.[25] NIH aggregates the enrollment data across the agency and reports this aggregate data to the Women's Health Advisory Committee, Congress, and the public in NIH's biennial inclusion report.

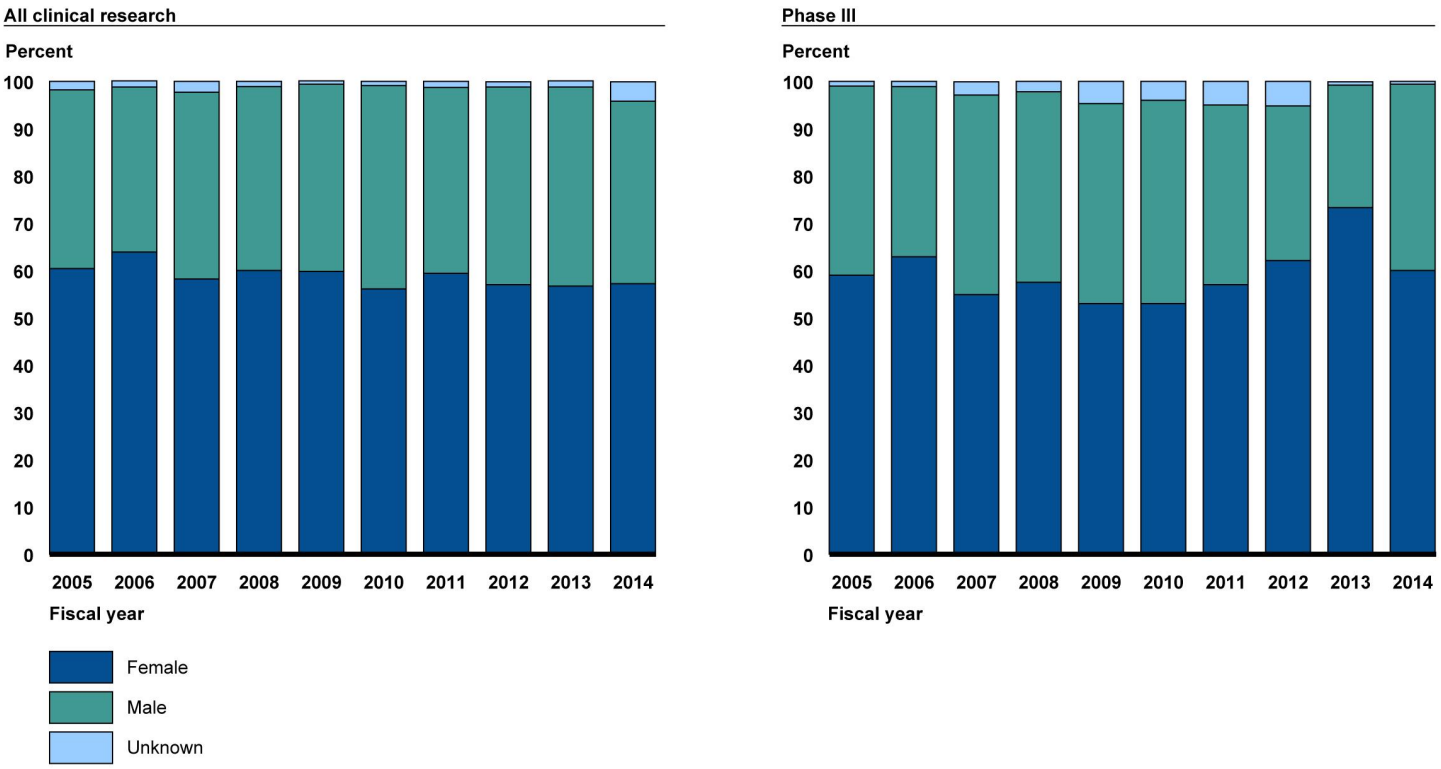
According to the data collected by NIH, in each fiscal year from 2005 through 2014, more women than men were enrolled in all NIH-funded clinical research studies, including phase III trials. (See fig. 1.) Specifically, in fiscal year 2014, among all NIH-funded clinical research studies, 57 percent of enrollees (16.4 million) were women, and 39 percent (11 million) were men.[26] For all NIH-funded phase III clinical trials, in fiscal year 2014, 60 percent of enrollees were women (about 480,000) and 39 percent were men (about 314,000).[27]

[25]For example, NIH officials told us they look for trends in enrollment across several years. According to the officials, if their review of trends reveals large shifts in enrollment, they will conduct additional analyses to determine whether one or more large studies may be contributing to the observed shifts in enrollment.

[26]The sex of 4 percent of enrollees across all NIH-funded clinical research studies was unknown.

[27]The sex of less than 1 percent of enrollees in NIH-funded phase III clinical trials was unknown.

**Figure 1: Enrollment in All National Institutes of Health (NIH) Funded Clinical Research by Sex, as a Percentage of Total Enrollment, Fiscal Years 2005-2014**




Source: GAO analysis of NIH data. | GAO-16-13

At the individual IC level, data show that for each IC, women's enrollment for all clinical research studies, including phase III clinical trials, was generally higher than men's enrollment in most years from fiscal year 2011 through fiscal year 2014. (See app. III for enrollment data at the NIH and IC level over this period.) Of the 25 ICs reporting enrollment in fiscal years 2011 through 2014, 13 ICs enrolled more women than men in the ICs' clinical research studies during all four years.[28] An additional 4 ICs

[28]Two ICs, the Center for Information Technology and the Center for Scientific Review, do not conduct or fund any clinical research studies or phase III trials, and thus, are not included in our discussion of IC enrollment. Additionally, we do not include the National Center for Research Resources in our IC discussion, as it ceased operations in fiscal year 2012, or the Office of Director and ORWH, as they are not ICs. However, each of these three entities funded clinical research or phase III trials in one or more years during the fiscal year 2013-2014 time period, and as such, their enrollment data are included in the totals for overall NIH clinical research studies and phase III trials.

enrolled more women than men in 3 of the fiscal years between 2011 and 2014. According to NIH, 10 of the 25 ICs regularly support phase III clinical trials, and of these, 3 (about one third) enrolled more women than men in each year in fiscal years 2011 through 2014, and another 2 enrolled more women than men in 3 of the 4 fiscal years.

## NIH Does Not Make IC-Level Enrollment Data Readily Available or Examine Detailed Enrollment Data to Identify Potential Challenges to Enrolling Women in Specific Research and Disease Areas

NIH collects and reviews aggregated enrollment data from the ICs; however, NIH officials do not make these IC-level enrollment data readily available to the public or other interested parties. Specifically, the IC-level enrollment data are not published as part of the overall NIH biennial report on enrollment, are not shared with the Women's Health Advisory Committee, and are not available for download from the ORWH website. Individual official IC enrollment reports were also not available through the websites of the three ICs in our review. Beginning in the fiscal year 2013-2014 reporting period, NIH required all ICs to submit their IC enrollment report numbers in a standard format, which may allow for easier public sharing of these data going forward.

Additionally, NIH officials do not routinely examine detailed enrollment data by sex beyond the IC level—such as by a specific research area or disease or condition being studied—to identify potential challenges to enrolling women in these areas, because enrollment data are currently not available in this format. The guidance NIH provided to the ICs for submitting their fiscal year 2013-2014 enrollment data to ORWH and OER explains that ICs may choose to further break out their reported enrollment data by disease area, portfolio area, or in some other manner. According to NIH officials, certain ICs analyze enrollment data by various disease categories when necessary. However, the IC officials we spoke with told us that their data systems are not capable of systematically aggregating enrollment data in this manner for routine reporting. When asked if it would be possible to aggregate enrollment data by disease and condition, IC officials said that they would be able to do so, but it would be a time intensive, manual process given current data system limitations. Further, NIH officials told us they expect NIH's new enrollment data system deployed in October 2014 to increase functionality in examining enrollment data in different ways, but as of July 2015 the officials did not have specific plans or details available. In addition, NIH officials stated that because an individual IC's research generally focuses on a specific disease, a particular organ, or a stage in life, the enrollment data that are aggregated at the IC level would roughly correspond with major disease and condition categories and could be used, to some extent, as a proxy for disease and condition enrollment data. However, this proxy method

does not take into account the fact that many ICs are responsible for research that includes multiple diseases, organs, or stages in life; for example, NHLBI's research portfolio includes studies of heart, lung, and blood related diseases and conditions. In addition, research on certain diseases and conditions—such as obesity—falls under the purview of multiple ICs.

NIH's practices of not sharing the IC-level enrollment data and not examining detailed data on enrollment by sex—by specific research area or the disease or condition being studied—are inconsistent with several federal standards for internal control.[29] Specifically, the internal control standards for information and communications state that for an entity to run and control its operations, it must have relevant, reliable, and timely communications relating to internal as well as external events. Information is needed throughout the agency to achieve all of its objectives, and effective communication should occur in a broad sense, with information flowing down, across, and up the organization. In addition to internal communications, management should ensure there are adequate means of communicating with, and obtaining information from, external stakeholders who may have a significant impact on the agency achieving its goals (e.g., the Women's Health Advisory Committee). Federal internal control standards for monitoring call for management to assess the quality of agency performance over time and ensure that the findings of audits and other reviews are promptly resolved.

Because NIH does not readily share IC-level enrollment data with the public and other interested parties, such as the Women's Health Advisory Committee—through means such as the ORWH website or the biennial NIH enrollment report—those interested in reviewing IC-level enrollment information would have to attend—or watch online if webcast—each individual IC's advisory board or council meeting or specifically seek out or request any public record resulting from these meetings to have access to these data. In addition, by not routinely examining more detailed enrollment data that is aggregated by sex—such as data at the disease and condition level—NIH is limited in its ability to identify whether women are sufficiently represented in studies in specific areas that cross ICs—such as obesity. Further, NIH does not have information of sufficient

[29]GAO/AIMD-00-21.3.1.

detail to monitor and determine if the aggregate enrollment data from across NIH inadvertently mask low enrollment for particular research areas or diseases or conditions. At an April 2015 Women's Health Advisory Committee meeting, some committee members raised such concerns, noting that published studies on clinical trials of specific diseases and conditions, such as cardiovascular disease, appeared to show that women's enrollment was lower than the enrollment that NIH had reported in the aggregate. The committee members acknowledged that there could be many reasons for such discrepancies, but noted that they would like to see more detailed enrollment data to improve their understanding of the data and ensure that women are being appropriately included in NIH-funded clinical trials.

## NIH Does Not Record Whether Clinical Trials Will Analyze Sex Differences to Allow Summary Analysis and Reporting for Oversight of Its Inclusion Policy

NIH's Inclusion Policy requires that individual awardees conducting phase III clinical trials consider whether analysis of potential differences in study outcomes between women and men is needed in their studies, consistent with the Revitalization Act's provisions regarding the design of certain clinical trials. However, the agency does not maintain, analyze, or report summary data to oversee whether analysis of outcomes by sex are planned or conducted, when applicable, across all NIH-funded clinical trials.

Under the Inclusion Policy, applicants seeking funds for phase III clinical trials must consider prior scientific evidence and assess whether an analysis of potential sex differences is merited, and if so, develop a plan to analyze study results accordingly.[30] Both this consideration and the plan for analysis, if appropriate, are to be included in the awardee's application for funding.[31] To ensure awardees' compliance with this

[30]NIH's policy states that awardees need to plan on conducting an analysis of potential sex differences if the findings of previous studies (1) support or (2) neither support nor negate the existence of sex differences. If prior studies support the existence of no significant differences, no further analysis is required.

[31]In June 2015, NIH announced plans for a revised policy requiring the consideration of sex as a biological variable in applications for studies of vertebrate animals and humans, stating that failing to account for sex as a biological variable in all biomedical research may undermine the rigor, transparency and generalizability of research findings. This revised policy will result in changes to fiscal year 2016 research grant applications, to be in effect for fiscal year 2017 funding. According to NIH, this change will not alter the existing Inclusion Policy, but over time, the change will build a better knowledge base about the influence of sex as a biological variable and better inform the design of clinical research going forward.

requirement, NIH officials told us they rely on the agency's peer review process for reviewing applications, and after awards are made, on IC program officers' monitoring of individual awardees. NIH has guidelines for peer reviewers to use when assessing applications and rating applicants' inclusion plans during peer review. This review typically includes an evaluation of the proposed study design and assessment of whether any plans for conducting an analysis of potential sex differences are "acceptable" or "unacceptable." The assessment and rating are based on consideration of prior scientific evidence that either supports or negates the existence of differences in outcomes by sex. Peer reviewers document this assessment in a summary statement provided to the ICs for final award determinations. According to NIH officials, if reviewers determine that an applicant's plans are not acceptable, the applicant is barred from funding until the plans are addressed and deemed acceptable by IC officials. After awards are made, program officers from the ICs that fund the studies are responsible for monitoring awardees' overall progress on an ongoing basis. Specifically, program officers are to review awardees' annual progress reports, which the Inclusion Policy states should address analysis of potential sex differences, as appropriate.[32] Officials from one IC told us that, through their regular interactions with awardees, program officers are very familiar with the design of their awardees' trials and whether any such analysis is planned or underway.

NIH program officers monitor individual awardees' compliance with the analysis requirement of the Inclusion Policy; however, the agency lacks summary data on awardees' analysis plans, including the percentage of awardees in a given year with trials designed to identify potential sex differences, when applicable. Currently, program officers review awardees' progress reports—including any information reported regarding the analysis of potential sex differences—but do not have means, such as a written checklist or a required field in an electronic reporting system, for recording the information obtained through this monitoring, as they do for monitoring enrollment. NIH's awardee data system includes information on whether individual awards include phase III trials. However, the data system does not have a data element that denotes whether an awardee's study should include or has plans for an analysis of potential sex

[32]The NIH guidance for awardees completing the annual progress report states "if analysis has begun or data has been published, report any progress made in evaluating potential differences by sex."

differences. Although such information is included in the narrative included in awardees' funding applications, this information cannot be easily aggregated for summary reporting, NIH officials explained, and therefore they do not estimate the proportion of trials being conducted at any one time that are designed and explicitly intended to identify differences in study outcomes by sex. NIH officials also told us that they plan to add a question for this type of monitoring to the existing electronic checklist used by program officers in the fall of this year, to be implemented for awards funded in fiscal year 2016.

Because NIH does not have summary data regarding the analysis requirement of the Inclusion Policy, it has not reported summary information on this aspect of the Inclusion Policy to key stakeholders—including the Women's Health Advisory Committee and the Congress. Notably, NIH's agency-wide biennial reports on the status of the Inclusion Policy do not include information on the extent to which NIH-funded phase III trials included plans to conduct analyses of potential sex differences, or on the overall status of this aspect of the Inclusion Policy. Instead, the report focuses primarily on NIH-wide aggregate enrollment.[33] NIH officials told us they rely on program officers' monitoring of individual awardees to ensure that the analysis requirement of the Inclusion Policy is being implemented appropriately after awards are made, because part of the program officer's role is to ensure satisfactory scientific progress as well as compliance with NIH policies. The officials added that they were not sure of the utility of summary reporting in this case.

NIH's lack of summary data and reporting regarding the analysis requirement of the Inclusion Policy conflicts with federal internal control standards.[34] First, federal internal control standards require that federal agencies have control activities in place to ensure that management's directives are carried out and that these controls are monitored. These standards also state that information should be recorded and communicated to management and other responsible officials in a form and within a time frame that enables them to carry out their internal control and other responsibilities.

[33]The report also includes information on the number of applications with inclusion plans considered acceptable and unacceptable at peer review, which NIH officials stated is an important part of ensuring compliance with this requirement.

[34]GAO/AIMD-00-21.3.1.

Without summary data on the funded phase III clinical trials that are intended to provide information on potential sex differences—including the number of such trials funded in a given year—senior NIH officials are limited in their ability to effectively oversee the implementation of the Inclusion Policy to assess whether changes are needed to their procedures. Further, NIH cannot provide this information to stakeholders such as the Women's Health Advisory Committee and Congress in its regular reporting on other aspects of the Inclusion Policy. As a result, these stakeholders lack assurance that the agency is implementing the Inclusion Policy as intended and in a manner consistent with the Revitalization Act's provisions regarding the design of certain clinical trials. In its fiscal year 2011-2012 *Report of the Advisory Committee on Research on Women's Health*, NIH previously acknowledged that inclusion is not just a matter of having women and men included in clinical studies; rather, the scientific value of research studies is greatly enhanced by providing knowledge about differences and/or similarities between different populations affected by the diseases under study. However, without assurance that its clinical trials are being designed and conducted as directed under the law and its implementing policy, NIH's insight regarding the interpretation, validation, and generalizability of findings resulting from the research it supports—as these findings apply to both women and men—is diminished, potentially limiting the value of NIH-funded research.

## Proposed NIH Policy Intended to Increase Public Reporting of Clinical Trial Results by Awardees and Could Increase Reporting of Sex-Specific Results, According to NIH Officials

NIH has developed and proposed a policy intended to increase public reporting of clinical trial results by requiring all NIH-funded clinical trials to be registered and have results submitted to its registry and results database, ClinicalTrials.gov.[35] ClinicalTrials.gov contains accessible and searchable information on publicly and privately supported clinical trials and observational studies that is provided and updated by NIH awardees and other researchers. Currently, all NIH awardees are encouraged to register their trials with ClinicalTrials.gov at the beginning of the study, but only certain trials—those of certain drugs and devices regulated by the Food and Drug Administration—must register and provide summary results as required by law.[36] According to NIH officials, as of July 2015, there were approximately 195,000 studies registered in ClinicalTrials.gov, and almost 18,000 of these have summary results information posted. Under the proposed NIH policy, all NIH-funded clinical trials, regardless of trial phase or type of intervention being studied, would have to be registered and submit summary results—including participant flow, baseline demographics such as the sex and age of participants, primary

[35]ClinicalTrials.gov was created in response to the Food and Drug Administration Modernization Act of 1997, which required HHS, through NIH, to establish a registry of clinical trials information for both federally and privately funded trials of experimental drugs for serious or life-threatening diseases or conditions. Pub. L. No. 105-115, § 113, 111 Stat. 2296, 2310-12 (Nov. 21, 1997) (codified as amended at 42 U.S.C. § 282(i)). NIH's National Library of Medicine manages ClinicalTrials.gov.

At the same time that NIH issued its proposed policy—in November 2014—HHS published for public comment a proposed rule to clarify and expand (as permitted) the Food and Drug Administration Amendments Act of 2007 requirements for certain clinical trials of Food and Drug Administration-regulated products to register and submit summary results to ClinicalTrials.gov. Pub. L. No. 110-85, § 801, 121 Stat. 823, 904-22 (Sept. 27, 2007) (codified as amended at 42 U.S.C. § 282(j)). NIH officials anticipate the final policy will be issued in the first quarter of fiscal year 2016.

[36]Applicable clinical trials subject to the ClinicalTrials.gov reporting requirements of the Food and Drug Administration Amendments Act of 2007 generally include: (1) trials of drugs: controlled clinical investigations—other than phase I investigations—of a drug subject to FDA regulation authorized by section 505 of the Federal Food Drug, and Cosmetic Act or section 351 of the Public Health Service Act, and (2) trials of devices subject to sections 510(k), 515, and 520(m) of the Federal Food, Drug, and Cosmetic Act: controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. Pub. L. No. 110-85, § 801, 121 Stat. 823, 904-22 (Sept. 27, 2007) (codified as amended at 42 U.S.C. § 282(j)).

and secondary outcomes, and adverse events—to ClinicalTrials.gov.[37] According to NIH, if the proposed policy goes into effect, compliance may be enforced through possible suspension or termination of funding and noncompliance could impact future funding decisions. NIH sought public comments on the proposed policy from November 2014 through March 2015 and, as of August 2015, was analyzing the comments it received. NIH anticipates that the final policy will be issued in the first quarter of fiscal year 2016.

NIH officials told us that the proposed policy for clinical trial registration and results submission was not intended to increase reporting of sex-specific results to ClinicalTrials.gov; however, the officials also said that there is the potential for more reporting of sex-specific results, given the overall increase expected in the number of reported studies. Since the proposed policy would require awardees to report results for their prespecified primary and secondary outcome measures as part of the summary results submission, the reporting of sex-specific results would depend on the design of the trial, according to NIH officials. Specifically, if sex differences were among the prespecified primary and secondary outcomes studied in a specific trial, officials said, then that would be reflected in the results submitted to ClinicalTrials.gov.

In issuing the proposed policy, NIH stated that its awardees are expected to make their trial results available to the research community and to the public at large in order to contribute to scientific knowledge and, ultimately, public health. NIH proposed the policy partly in response to a recent study, which found that within 30 months of trial completion, the results of less than half of NIH-funded clinical trials had been published in a peer-reviewed biomedical journal, the traditional method for sharing results.[38] NIH stated that because journal publication of clinical trials results is not always possible, it is important to provide other ways for clinical trial results to be disseminated and publicly available to researchers, health care providers, and others.

[37]Participant flow is a description of the number of research participants starting and completing the study. HHS defines as “primary” the outcome measure that is considered the most important, although more than one may be appropriate under specific circumstances. The proposed definition of “secondary outcome measure” would include all pre-specified outcome measures that are not designated as “primary” and for which a specific analysis plan exists, either in the protocol or the statistical analysis plan.

[38]J. S. Ross, et al. “Publication of NIH funded trials.”

NIH has made efforts to encourage sex-specific reporting of clinical trial results. In NIH's fiscal years 2011-2012 *Report on the Advisory Committee for Research on Women's Health*, ORWH stated that it is only through sex-specific reporting that full information becomes available to the public and to scientists who can then use such data to inform future studies, thereby building the knowledge base in a manner that takes into consideration the influences of sex on health and disease. Specifically, NIH has worked with journal editors and others to encourage reporting of results by sex. Specifically, in 2011, NIH asked IOM to convene a workshop of researchers, journal editors, and others on the topic to discuss the importance of reporting results by sex and the implications of this issue for journals' reporting policies. According to Stanford University's Gendered Innovations project, 32 peer-reviewed journals worldwide have editorial policies requiring that clinical trial researchers include information on results by sex when they submit articles for publication.[39] However, editors from one medical journal that we spoke with stated that when evaluating whether results should be reported by sex, it is important to consider whether examining sex differences is a primary outcome of the study, and whether the trial was big enough for a valid subgroup analysis—i.e., analysis of the effect of the intervention on two or more different groups of participants, such as women and men. They emphasized that if a study was not designed for a subgroup analysis by sex and one was performed, the results could be erroneous.

NIH has also made efforts to facilitate the sharing of clinical trials results, including sex-specific information, through venues other than journals and ClinicalTrials.gov. NIH has a number of policies that promote the dissemination of research results—and the underlying data—and guide awardees in disseminating their results, including the NIH Data Sharing Policy, among others.[40] Additionally, related to the sharing of sex-specific information, NIH hosts a Women's Health Resources portal and a Women's Health topic page on the Medline Plus webpage, which includes links to other information about women's health from journal articles and ClinicalTrials.gov. The agency also reports summaries of research related

[39]The Gendered Innovations project was initiated at Stanford University in 2009 to provide scientists and engineers with practical methods for sex and gender analysis. Gendered Innovations involves experts from across the U.S. and the European Union.

[40]Other NIH data sharing policies include the NIH Public Access Policy, the NIH Model Organism and Related Resources Sharing Policy, and the NIH Genomic Data Sharing Policy.

to women's health in the biennial *Report of the Advisory Committee on Research on Women's Health*.

## Conclusions

Although NIH has made progress in the 2 decades since the 1993 Revitalization Act regarding the inclusion of women in NIH-funded clinical research, opportunities remain for NIH to further extend the value of its investment in medical research. NIH is responsible for ensuring that the nation receives the greatest benefit of the large federal investment in clinical research by fully implementing its Inclusion Policy, such that women are adequately included in NIH-funded clinical trials when appropriate, and that potential sex differences may be identified. By not readily sharing IC-level enrollment data, NIH limits the public's and other interested parties' ability to gain insight into enrollment issues at each of the ICs, putting the onus of obtaining these data on the interested parties themselves to attend or view online up to 25 individual IC board or council meetings or request any public record of these meetings. By not examining more detailed enrollment data—such as data aggregated by research area or specific to various diseases and conditions—NIH cannot know whether it is adequately including women across all of the research it supports. Without this greater insight into enrollment for specific to diseases and conditions, NIH is limited in its ability to assess whether its programs that support cross-cutting research spanning multiple ICs are successfully including women in clinical research or facing challenges that the agency should address. Further, the lack of summary data and reporting about the extent to which awardees plan to conduct or perform analyses of potential sex differences in phase III clinical trials compromises NIH's oversight and jeopardizes the agency's ability to provide assurances over the Act's provisions regarding the design of certain clinical trials and meet the purposes of its Inclusion Policy. Without summary data, such as the proportion of trials being conducted that intend to analyze differences in outcomes for men and women, and reporting on that data, NIH and Congress cannot know whether or to what extent current efforts are helping to ensure that differences in clinical outcomes by sex are identified and that NIH is supporting research that can be used to shape improved medical practices for both women and men.

The overall increase in the enrollment of women in NIH-funded clinical research studies, such that women have been a significant proportion of research subjects for nearly 2 decades, is a noteworthy achievement for NIH. To continue to build on this achievement—and consistent with federal internal control standards—NIH should turn its focus to assessing

whether the agency is meeting the purposes of the Inclusion Policy, and if it is not, take the needed corrective actions.

## Recommendations for Executive Action

To ensure effective implementation of the Inclusion Policy in a manner consistent with the Revitalization Act's provisions regarding the design of certain clinical trials, the NIH Director should take the following five actions:

- make IC-level enrollment data readily available through public means, such as NIH's regular biennial report to Congress on the inclusion of women in research, or through NIH's website;
- examine approaches for aggregating more detailed enrollment data at the disease and condition level, and report on the status of this examination to key stakeholders and through its regular biennial report to Congress on the inclusion of women in research;
- ensure that program officers have a means for recording information obtained from monitoring awardees' plans for and progress in conducting analyses of potential differences in outcomes by sex;
- on a regular basis, systematically collect and analyze summary data regarding awardees' plans to conduct analyses of potential sex differences, such as the proportion of trials being conducted that intend to analyze differences in outcomes for men and women; and
- report on this summary data and the results of this analysis in NIH's regular biennial report to Congress on the inclusion of women in research.

## Agency Comments and Our Evaluation

We provided a draft of this product to HHS for comment, and HHS responded with comments provided by NIH. In its written comments, reproduced in appendix IV, NIH generally concurred with our findings and recommendations. NIH also provided technical comments that were incorporated into the final report, as appropriate.

In commenting on our first recommendation to make IC-level enrollment data readily available to the public, NIH agreed and indicated that there are opportunities for the agency to increase the accessibility of IC-level enrollment data. NIH also stated that the agency has begun to standardize IC enrollment reporting and will continue this effort by standardizing data tables and graphics for ICs to provide for the NIH-wide

biennial reports. NIH did not provide a timeline for making this information readily available to the public.

NIH agreed with our second recommendation to examine approaches for aggregating more detailed enrollment information at the disease and condition level, and to report on the status of this examination to key stakeholders. In its comments, NIH also reiterated what we describe in our report: some ICs conduct analysis of enrollment by disease or condition on an as-needed basis. NIH noted that the agency is working on ways to analyze enrollment at the disease and condition level across the ICs. NIH did not provide information on when the agency would be able to analyze these enrollment data, but it did state that when the agency is able to perform the analysis, NIH would make the results readily available through NIH's biennial inclusion reports or other means.

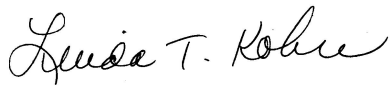
NIH agreed with our third recommendation to ensure that program officers have a means for recording their monitoring of awardees' plans for and progress in conducting analysis of potential sex differences, and confirmed that the agency plans to add questions that would facilitate this type of monitoring into the existing checklist program officers use to document other types of monitoring beginning in fiscal year 2016.

In commenting on our fourth and fifth recommendations regarding collecting and reporting summary data on awardees' plans for sex-differences analysis, NIH agreed that it is critical to obtain more information on which clinical trials involve analyses of sex differences, and described some alternative data collection approaches for improving oversight of this issue. We maintain that thoughtful, useful analysis and summary reporting would improve NIH's oversight of this aspect of the Inclusion Policy. Our recommendation was not intended to prescribe or limit the type of analysis performed or the data collected by NIH; instead we provided an example that NIH could adapt as needed, and we encourage the agency to explore the best alternatives for their analyses.

In other general comments, NIH also noted other opportunities that support oversight, such as the importance of peer reviewers in examining applicants' plans for including women prior to funding decisions, and expanded reporting in ClinicalTrials.gov. In addition, the agency noted that ClinicalTrials.gov could engender greater transparency of clinical trial results and help assure that the analyses required under the Inclusion Policy are being completed.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies of this report to the Secretary of the Department of Health and Human Services, the Director of the National Institutes of Health, and other interested parties. In addition, the report will be available at no charge on the GAO Web site at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or at kohnl@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix V.



Linda T. Kohn
Director, Health Care

*List of Requesters*

The Honorable Barbara Mikulski
Ranking Member
Committee on Appropriations
United States Senate

The Honorable Patty Murray
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce
House of Representatives

The Honorable Kirsten Gillibrand
United States Senate

The Honorable Debbie Stabenow
United States Senate

The Honorable Elizabeth Warren
United States Senate

The Honorable Lois Capps
House of Representatives

The Honorable Rosa L. De Lauro
House of Representatives

The Honorable Nita Lowey
House of Representatives

# Appendix I: Literature Review of Factors Affecting Women's Participation in Clinical Research

We reviewed 34 published journal articles that specifically identified barriers to or reasons for women's participation in clinical research. We conducted an initial literature search that identified 168 studies published from January 2004 through October 2014 on the topic of women in clinical research.[1] After reviewing abstracts and the full text of some articles, we narrowed this group down to the 34 articles included in this report that focus on the factors specifically affecting women's participation in clinical research.[2] We also spoke with or received written responses from officials and program officers from 3 institutes and centers (ICs) of the National Institutes of Health (NIH) about the factors affecting women's participation in clinical research reported by NIH awardees.

In our review of the literature, the three most commonly cited barriers women face when considering whether to participate in clinical research were fear of experimentation/trust issues, health related concerns, and transportation/convenience issues. (See table 1.) Fear of experimentation/trust issues included distrust of physicians and the medical community and fear that the experimental treatment may be inferior to the conventional treatment(s). Health related concerns cited in the articles included concerns about the potential side effects or other adverse events associated with the experimental treatment. Some of the transportation/convenience concerns cited in the articles included difficulty traveling to a clinic (no transportation or a long distance to the facility) and general inconvenience associated with participating in the research.

[1]We conducted a search of relevant databases—including MEDLINE, BIOSIS Previews, Embase, International Pharmaceutical Abstracts, NTIS: National Technical Information Service, PAIS International, PsycINFO, Sociological Abstracts, PapersFirst, WorldCat, and CINAHL—using search terms related to women and clinical trials. The search also focused on articles on U.S.-based populations.

[2]We reviewed abstracts for all 168 articles, as available, and selected 71 articles for review of the full text.

**Table 1: Types of Barriers Identified for Women in Literature Review**

| Barrier Type | Number of Articles |
|---|---|
| Fear of experimentation/trust concerns | 19 |
| Health related concerns | 19 |
| Transportation/convenience issues | 16 |
| Other | 15 |
| Trial/study related concerns | 13 |
| Lack of or competing interests | 12 |
| Work/financial reasons | 9 |
| Home and family responsibilities | 8 |
| Cultural concerns/language issues | 6 |
| Lack of knowledge about research | 5 |
| Stigma | 4 |

Source: GAO literature review. | GAO-16-13

The three most common reasons for women's participation in clinical research identified in our literature review were personal/health benefits, altruism, and a general category of "other" reasons. (See table 2.) Personal/health benefits included access to new treatment and drugs, while "other" reasons included the fact that the research was being done at a clinic where the participant had already received care or was being conducted by clinical staff with whom the participants were familiar. Participation due to altruism included the desire to help science.

**Table 2: Types of Reasons to Participate Identified for Women in Literature Review**

| Types of Reasons to Participate | Number of Articles |
|---|---|
| Personal/health benefits | 18 |
| Other | 15 |
| Altruism | 14 |
| Financial benefits | 11 |
| Family/medical support and encouragement | 10 |
| Free care/services/treatment | 6 |
| Interest in research | 5 |

Source: GAO literature review. | GAO-16-13

The NIH IC officials and program officers we spoke with generally agreed that the barriers and reasons for participation that we identified through our literature review were consistent with those they have encountered when working with their awardees. In addition, officials from one IC we spoke with identified other reasons women participate in clinical research, as cited by awardees. These reasons included the opportunity to learn about the disease being studied and how to manage it, and a sense of pride associated with participation. In contrast, these officials stated that for some diseases, the effect or perceived effect on future fertility could be a barrier to women's participation.

# Appendix II: National Institutes of Health (NIH) Funding for Women's Health Research

To determine the amount of NIH funding for research on women's health, we collected and reviewed NIH women's health budget information for fiscal years 2009-2014. We also interviewed officials from NIH and the Department of Health and Human Services (HHS) regarding the budget categories that NIH uses in its women's health budget, which were originally developed for use in reporting by all HHS agencies.

NIH, like all HHS agencies, annually compiles a summary table that estimates funding for women's health research. Per HHS's guidance, NIH classifies its funding into 16 categories and about 120 sub-categories representing specific diseases and conditions; and three categories by sex—funding for women's health research, funding for men's health research, and funding for research related to both women's and men's health. Since the sex categorization of funding is based on enrollment, a portion of funding for research studies for certain diseases that primarily affect women—such as cervical cancer—but are reported as including male participants may be categorized as related to men's health or both sexes. NIH reports these funding estimates in HHS's annual congressional budget justification and in the biennial *Report of the Advisory Committee on Research on Women's Health*.[1]

To more closely examine the amount NIH funded for research on selected diseases and conditions with a particular relevance to women, we developed a list of diseases and conditions using the top 10 diseases and conditions in each of the Centers for Disease Control and Prevention's 2012 lists of leading causes of death for women and leading chronic diseases for women. We supplemented this information with the diseases and conditions with a particular relevance to women that were identified in a 2010 Institute of Medicine report, *Women's Health Research: Progress, Pitfalls, and Promise*.[2]

We worked with NIH and several of its institutes and centers (IC) to assign each of the diseases and conditions in our list to the NIH budget categories that were included in the women's health budget. These

[1]For a link to the report, visit http://orwh.od.nih.gov/about/acrwh/index.asp, which we accessed July 21, 2015.

[2]Institute of Medicine, *Women's Health Research: Progress, Pitfalls, and Promise* (Washington, DC: The National Academies Press, 2010).

matches allowed us to provide an estimate of funding for these selected diseases and conditions, which are shown in Table 3.

NIH officials told us that determining the amount NIH funded for women's health research overall—as well as for specific diseases and conditions—is difficult, and the resulting information are estimates, rather than actual amounts, due to challenges compiling the funding data. These challenges include: (1) methodological issues in assigning research funding to a sex category, especially for basic research, which does not include human subjects, (2) difficulties assigning NIH research funding to broad HHS-determined disease categories, (3) research projects that overlap disease categories, but must be assigned to a single disease category, and (4) variation in data collection processes at the IC level.

**Table 3: National Institutes of Health (NIH) Estimated Funding for Selected Diseases and Conditions with a Particular Relevance to Women, Fiscal Year 2014**

| | | | NIH women's health research category(s) funding in thousands | | | |
|---|---|---|---|---|---|---|
| **Disease or condition** | **NIH women's health research category(s)** | **Whether category(s) is a direct match** [Note A] | **Women** | **Men** | **Both** | **Total** |
| Accidents (unintentional injuries) | Unintentional injury | Yes | $230 | 636 | 24,257 | **25,123** |
| Alcohol and drug addiction | Alcohol | — | $20,096 | 22,693 | 113,472 | **156,261** |
| | Illegal drugs | — | $125,522 | 129,360 | 221,170 | **476,052** |
| | Subtotal | No [Note B] | $145,618 | 152,053 | 334,642 | **632,313** |
| Alzheimer's disease | Alzheimer's disease | Yes | $106,729 | 88,825 | 304,141 | **499,695** |
| Arthritis diagnosis | No corresponding category | N/A | N/A | N/A | N/A | **N/A** |
| Asthma | Asthma | Yes | $49,078 | 48,546 | 128,323 | **225,947** |
| Autoimmune diseases | Lupus erythematosus | — | $44,836 | 4,669 | 27,151 | **76,656** |
| | Multiple sclerosis | — | $5,672 | 11,072 | 66,929 | **83,673** |
| | Scleroderma | — | $12,336 | 102 | 2,441 | **14,879** |
| | Sjogren's syndrome | — | $17,458 | 0 | 375 | **17,833** |
| | Diabetes | — | $106,607 | 76,701 | 88,563 | **271,871** |
| | Immune disorders: other | — | $517 | 396 | 184,372 | **185,285** |
| | Subtotal | No [Note B] | $187,426 | 92,940 | 369,831 | **650,197** |
| Breast cancer | Breast cancer | Yes | $705,090 | 68 | 1,430 | **706,588** |
| Cervical cancer | Reproductive cancers: cervical | Yes | $84,966 | 1,108 | 6,700 | **92,774** |
| Chronic fatigue syndrome | Chronic fatigue syndrome | Yes | $1,668 | 790 | 632 | **3,090** |
| Chronic joint symptoms | Chronic pain conditions | No [Note C] | $3,948 | 10,500 | 120,601 | **135,049** |
| Chronic lower respiratory diseases | Asthma | No [Note D] | $49,078 | 48,546 | 128,323 | **225,947** |
| | Pulmonary diseases | | $82,792 | 83,493 | 333,214 | **499,499** |
| Chronic pain conditions | Chronic pain conditions | Yes | $3,948 | 10,500 | 120,601 | **135,049** |
| Colorectal cancer | Colorectal cancer | Yes | $131,348 | 231 | 129,825 | **261,404** |
| Depression | Depression/mood disorders | No [Note C] | $20,219 | 2,708 | 118,513 | **141,440** |
| Diabetes mellitus | Diabetes | Yes | $106,607 | 76,701 | 88,563 | **271,871** |
| Eating Disorders | Eating disorders | Yes | $4,924 | 0 | 6,315 | **11,239** |
| Fibromyalgia | Fibromyalgia and eosinophilic myalgia | No [Note C] | $3,652 | 0 | 0 | **3,652** |

| Disease or condition | NIH women's health research category(s) | Whether category(s) is a direct match [Note A] | NIH women's health research category(s) funding in thousands | | | |
|---|---|---|---|---|---|---|
| | | | Women | Men | Both | Total |
| Gynecologic cancers other than cervical cancer | Reproductive cancers: ovarian | — | $111,573 | 0 | 0 | **111,573** |
| | Reproductive cancers: vaginal, uterine and other | — | $25,489 | 0 | 0 | **25,489** |
| | Subtotal | No [Note B] | $137,062 | 0 | 0 | **137,062** |
| Hearing trouble | Ear diseases and disorders | No [Note C] | $12,514 | 7 | 215,658 | **228,179** |
| HIV/AIDS | AIDS/HIV | Yes | $167,978 | 71,539 | 2,228,561 | **2,248,078** |
| Hypertension | Heart disease | No [Note D] | $125,873 | 121,968 | 790,991 | **1,038,832** |
| | Other cardiovascular diseases/disorders | | $132,560 | 102,727 | 791,654 | **1,026,941** |
| Incontinence | Urinary incontinence | — | $7,772 | 0 | 0 | **7,772** |
| | Fecal incontinence | — | $1,179 | 131 | 0 | **1,310** |
| | Subtotal | No [Note B] | $8,951 | 131 | 0 | **9,082** |
| Influenza and pneumonia | Global health | No [Note C] | $11,509 | 67,485 | 1,788,623 | **1,867,617** |
| Irritable bowel syndrome | Irritable bowel syndrome | Yes | $7,962 | 815 | 749 | **9,526** |
| Lower back pain | Chronic pain conditions | No [Note C] | $3,948 | 10,500 | 120,601 | **135,049** |
| Lung cancer | Lung cancer | Yes | $150,678 | 230 | 119,998 | **270,906** |
| Major cardiovascular diseases | Heart disease | No [Note C] | $125,873 | 121,968 | 790,991 | **1,038,832** |
| Malignant neoplasms | Cancer (ALL) | Yes | $2,246,960 | 79,466 | 4,010,650 | **5,337,076** |
| Maternal mortality and morbidity | Pregnancy/pregnancy prevention/maternal health | No [Note C] | $225,407 | 741 | 14,663 | **240,811** |
| Melanoma | Other neoplasms | No [Note C] | $37,816 | 77,829 | 3,752,697 | **3,868,342** |
| Memory and cognitive changes associated with perimenopause | Menopause | No [Note C] | $24,945 | 0 | 200 | **25,145** |
| Mental illness other than depression | Mental health (ALL minus depression/mood disorders) | No [Note E] | $55,169 | 43,437 | 1,108,536 | **1,207,142** |
| Migraines | Migraine | Yes | $50 | 50 | 856 | **956** |
| Neck Pain | Chronic pain conditions | No [Note C] | $3,948 | 10,500 | 120,601 | **135,049** |
| Nephritis, nephrotic syndrome and nephrosis | Kidney and urologic: Other | No [Note C] | $1,438 | 5,845 | 407,939 | **415,222** |

| Disease or condition | NIH women's health research category(s) | Whether category(s) is a direct match [Note A] | NIH women's health research category(s) funding in thousands | | | |
|---|---|---|---|---|---|---|
| | | | Women | Men | Both | Total |
| Non-malignant gynecological disorders | Endometriosis/ leiomyomas | — | $8,238 | 0 | 417 | **8,655** |
| | Pelvic floor disorders | — | $1,223 | 0 | 0 | **1,223** |
| | Female reproductive physiology | — | $64,968 | 0 | 0 | **64,968** |
| | Subtotal | No [Note B] | $74,429 | 0 | 417 | **74,846** |
| Osteoporosis | Osteoporosis (including fractures) | Yes | $88,553 | 7,214 | 10,956 | **106,723** |
| Other diseases of the respiratory system | Pulmonary diseases | No [Note C] | $82,792 | 83,493 | 333,214 | **499,499** |
| Pregnancy-related issues | Pregnancy/pregnancy prevention/maternal health | No [Note C] | $225,407 | 741 | 14,663 | **240,811** |
| Septicemia | Blood diseases | No [Note C] | $37,646 | 47,807 | 415,524 | **500,977** |
| Sexual dysfunction | No corresponding category | N/A | N/A | N/A | N/A | **N/A** |
| Sinusitis | Infectious diseases: other | No [Note C] | $1,523 | 822 | 650,482 | **652,827** |
| Stress-related disorders | Psychosocial stress | No [Note C] | $6,129 | 865 | 20,795 | **27,789** |
| Thyroid disease | Thyroid diseases/conditions | No [Note C] | $11,184 | 2,796 | 0 | **13,980** |
| Type 2 diabetes | Diabetes | No [Note C] | $106,607 | 76,701 | 88,563 | **271,871** |
| Unintended pregnancy | Pregnancy/pregnancy prevention/maternal health | No [Note C] | $225,407 | 741 | 14,663 | **240,811** |

Sources: GAO analysis of NIH data. | GAO-16-13

Notes: According to NIH, funding figures are categorized as either inseparably combined—in the "Both" category—or as related to research on women's health or men's health. In cases in which NIH did not believe that a GAO-identified disease or condition could be linked to an NIH budget category, the NIH Research Category is labeled as "N/A" for not applicable.

Note A: A "yes" in this column indicates that the GAO-identified category and the HHS-defined category are identical or nearly identical.

Note B: NIH officials stated that this GAO-identified disease or condition represented multiple NIH budget categories, so funding figures for all categories are listed. The categories were summed and are also represented as a subtotal.

Note C: The funding figure listed for research on this GAO-identified disease or condition is an estimate based on the closest category match possible. Actual funding may be less or more than the dollar amount listed.

Note D: NIH officials stated that this GAO-identified disease or condition could be assigned to one of two categories, so funding figures for both categories are listed.

Note E: NIH officials stated that this GAO-identified disease or condition represented the larger "Mental Health" category, minus the subcategory of "Depression/Mood disorders," so we calculated this figure accordingly to present a single amount.

# Appendix III: National Institutes of Health (NIH) and Institute and Center (IC) Research Study Enrollment

Tables 4 and 5 below present NIH and IC-level enrollment data, by sex, for fiscal years 2011 through 2014—for all clinical research studies and for phase III clinical trials, respectively.

**Table 4: Percentage Female, Male, and Other Enrollment in All Clinical Research Studies, for NIH Overall and Institutes and Centers (IC), Fiscal Years 2011-2014**

| | | All NIH clinical research | | | |
|---|---|---|---|---|---|
| **NIH or IC** | | **2011** | **2012** | **2013** | **2014** |
| NIH, overall | Female | 59.4 | 57.0 | 56.7 | 57.2 |
| | Male | 39.3 | 41.8 | 42.1 | 38.6 |
| | Other | 1.3 | 1.1 | 1.3 | 4.1 |
| Fogarty International Center | Female | 49.9 | 47.1 | 60.3 | 60.7 |
| | Male | 48.5 | 51.8 | 38.3 | 38.5 |
| | Other | 1.7 | 1.1 | 1.5 | 0.8 |
| National Cancer Institute | Female | 61.7 | 55.7 | 57.1 | 60.9 |
| | Male | 37.8 | 44.0 | 42.5 | 35.1 |
| | Other | 0.5 | 0.3 | 0.4 | 4.1 |
| National Center for Advancing Translational Sciences [Note A] | Female | 0.0 | 59.0 | 36.7 | 0.0 |
| | Male | 0.0 | 41.0 | 63.3 | 0.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Center for Complementary and Integrative Health | Female | 47.2 | 63 | 62.5 | 64 |
| | Male | 51.8 | 34.1 | 28.4 | 27.7 |
| | Other | 0.9 | 2.9 | 9.1 | 8.2 |
| National Eye Institute | Female | 51.6 | 52.3 | 55.9 | 56.2 |
| | Male | 47.8 | 46.7 | 43.7 | 43.7 |
| | Other | 0.6 | 1.0 | 0.4 | 0.1 |
| National Heart, Lung, and Blood Institute | Female | 47.9 | 57.7 | 57.5 | 49.9 |
| | Male | 50.2 | 41.1 | 41.5 | 48.6 |
| | Other | 1.9 | 1.3 | 1.0 | 1.5 |

| NIH or IC | | All NIH clinical research | | | |
|---|---|---|---|---|---|
| | | 2011 | 2012 | 2013 | 2014 |
| National Human Genome Research Institute | Female | 54.4 | 45.4 | 46.3 | 48.5 |
| | Male | 36.6 | 43.9 | 50.5 | 51 |
| | Other | 9.0 | 10.7 | 3.2 | 0.5 |
| National Institute on Aging | Female | 54.1 | 54.4 | 51.7 | 53.2 |
| | Male | 45.4 | 44.7 | 44.4 | 43.5 |
| | Other | 0.5 | 0.9 | 3.9 | 3.3 |
| National Institute on Alcohol Abuse and Alcoholism | Female | 46.8 | 46.6 | 45.3 | 44.3 |
| | Male | 52.9 | 52.9 | 53.0 | 55.2 |
| | Other | 0.3 | 0.5 | 1.7 | 0.6 |
| National Institute of Allergy and Infectious Diseases | Female | 48.0 | 50.6 | 49.8 | 50.9 |
| | Male | 50.6 | 47.4 | 48.5 | 48.8 |
| | Other | 1.3 | 2.0 | 1.7 | 0.3 |
| National Institute of Arthritis and Musculoskeletal and Skin Diseases | Female | 58.9 | 57.0 | 57.8 | 56.6 |
| | Male | 38.8 | 41.8 | 41.3 | 43.0 |
| | Other | 2.3 | 1.2 | 0.8 | 0.4 |
| National Institute of Biomedical Imaging and Bioengineering | Female | 63.6 | 52.9 | 64 | 64.1 |
| | Male | 35.1 | 44.8 | 34.8 | 35.6 |
| | Other | 1.3 | 2.3 | 1.1 | 0.3 |
| Eunice Kennedy Shriver National Institute of Child Health and Human Development | Female | 66.7 | 74.1 | 71.6 | 58.3 |
| | Male | 31.8 | 24.5 | 27.1 | 26.9 |
| | Other | 1.5 | 1.4 | 1.3 | 14.8 |
| National Institute on Deafness and Other Communication Disorders | Female | 50.0 | 52.1 | 48.4 | 47.4 |
| | Male | 49.9 | 47.0 | 50.7 | 51.9 |
| | Other | 0.2 | 0.9 | 1.0 | 0.6 |
| National Institute of Dental and Craniofacial Research | Female | 56.6 | 57.3 | 58.9 | 52.3 |
| | Male | 40.4 | 39.0 | 37.0 | 38.9 |
| | Other | 3.0 | 3.7 | 4.1 | 8.9 |
| National Institute of Diabetes and Digestive and Kidney Diseases | Female | 57.1 | 54.6 | 53.5 | 54.8 |
| | Male | 41.9 | 44.3 | 45.7 | 43.9 |
| | Other | 1.1 | 1.1 | 0.9 | 1.3 |
| National Institute on Drug Abuse | Female | 45.8 | 46.3 | 46.8 | 41.0 |
| | Male | 49.5 | 48.8 | 50.3 | 57.0 |
| | Other | 4.7 | 4.9 | 2.9 | 2.0 |
| National Institute of Environmental Health Sciences | Female | 73.5 | 71.8 | 69.9 | 73.0 |
| | Male | 26.2 | 28.1 | 29.9 | 26.8 |
| | Other | 0.3 | 0.2 | 0.2 | 0.2 |

| NIH or IC | | All NIH clinical research | | | |
|---|---|---|---|---|---|
| | | 2011 | 2012 | 2013 | 2014 |
| National Institute of General Medical Sciences | Female | 54.8 | 62.8 | 54.0 | 80.2 |
| | Male | 44.8 | 35.6 | 43.8 | 18.6 |
| | Other | 0.3 | 1.6 | 2.2 | 1.2 |
| National Institute of Mental Health | Female | 52.7 | 47.0 | 42.6 | 49.6 |
| | Male | 45.8 | 51.4 | 56.0 | 49.5 |
| | Other | 1.5 | 1.7 | 1.4 | 0.9 |
| National Institute of Minority Health and Health Disparities | Female | 60.2 | 63.4 | 70.4 | 59.1 |
| | Male | 38.8 | 35.1 | 29.0 | 38.9 |
| | Other | 1.0 | 1.5 | 0.6 | 2.1 |
| National Institute of Neurological Disorders and Stroke | Female | 51.3 | 50.3 | 53.6 | 53.8 |
| | Male | 45.2 | 44.4 | 43.7 | 44.3 |
| | Other | 3.5 | 5.3 | 2.6 | 1.9 |
| National Institute of Nursing Research | Female | 60.4 | 59.9 | 59.2 | 65.8 |
| | Male | 38.3 | 38.2 | 40.5 | 33.5 |
| | Other | 1.4 | 2.0 | 0.4 | 0.7 |
| National Library of Medicine | Female | 59.6 | 48.2 | 54.7 | 44.9 |
| | Male | 40.4 | 51.8 | 45.2 | 52.2 |
| | Other | 0.0 | 0.0 | 0.1 | 3.0 |
| NIH Clinical Center | Female | 38.5 | 38.1 | 38.0 | 36.6 |
| | Male | 42.5 | 42.1 | 44.0 | 44.4 |
| | Other | 19.1 | 19.8 | 18.0 | 19.0 |

Source: NIH. | GAO-16-13

Notes: Two ICs, the Center for Information Technology and the Center for Scientific Review, do not conduct or fund any clinical research studies, and thus, are not included in this table. Additionally, we do not include the National Center for Research Resources in this table, as it ceased operations in fiscal year 2012, or the Office of Director and Office of Research on Women's Health, as they are not ICs. However, each of these three entities funded clinical research in one or more years during the fiscal year 2011-2014 time period, and as such, their enrollment data are included in the totals for overall NIH clinical research studies. "Other" enrollment includes participants whose sex was not reported or is otherwise unknown.

Note A: IC did not begin operations until fiscal year 2012 and maintains a very small portfolio of clinical research.

**Table 5: Percentage Female, Male, and Other Enrollment in Phase III Clinical Trials, for NIH Overall and Institutes and Centers (IC), Fiscal Years 2011-2014**

| NIH or IC | | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| NIH, overall | Female | 57.0 | 62.1 | 73.3 | 60.0 |
| | Male | 38.0 | 32.7 | 25.9 | 39.4 |
| | Other | 5.0 | 5.2 | 0.7 | 0.6 |
| Fogarty International Center [Note A] | Female | 0.0 | 0.0 | 0.0 | 0.0 |
| | Male | 0.0 | 0.0 | 0.0 | 0.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Cancer Institute | Female | 61.4 | 62.1 | 81.1 | 61.7 |
| | Male | 38.5 | 37.8 | 18.8 | 38.2 |
| | Other | 0.0 | 0.1 | 0.0 | 0.1 |
| National Center for Advancing Translational Sciences [Notes A and B] | Female | 0.0 | 0.0 | 0.0 | 0.0 |
| | Male | 0.0 | 0.0 | 0.0 | 0.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Center for Complementary and Integrative Health [Note C] | Female | 0.0 | 0.0 | 0.0 | 54.1 |
| | Male | 0.0 | 0.0 | 0.0 | 45.9 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Eye Institute | Female | 47.8 | 48.6 | 62.3 | 56.8 |
| | Male | 52.2 | 51.4 | 37.7 | 43.2 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Heart, Lung, and Blood Institute | Female | 49.8 | 41 | 42.7 | 44.9 |
| | Male | 50.2 | 58.9 | 57.3 | 55.1 |
| | Other | 0.0 | 0.1 | 0.0 | 0.0 |
| National Human Genome Research Institute [Notes A and D] | Female | 0.0 | 0.0 | 0.0 | 0.0 |
| | Male | 0.0 | 0.0 | 100.0 | 100.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Institute on Aging [Note C] | Female | 54.7 | 0.0 | 50.5 | 75.1 |
| | Male | 45.3 | 0.0 | 49.5 | 24.9 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Institute on Alcohol Abuse and Alcoholism [Note C] | Female | 0.0 | 0.0 | 81.1 | 79.3 |
| | Male | 0.0 | 0.0 | 18.9 | 19.2 |
| | Other | 0.0 | 0.0 | 0.0 | 1.5 |
| National Institute of Allergy and Infectious Diseases | Female | 37.8 | 42.6 | 51.4 | 45.8 |
| | Male | 62.2 | 57.4 | 48.6 | 54.2 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Institute of Arthritis and Musculoskeletal and | Female | 50.0 | 50.0 | 50.0 | 50.0 |
| | Male | 50.0 | 50.0 | 50.0 | 50.0 |

| NIH or IC | | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| Skin Diseases [Note C] | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Institute of Biomedical Imaging and Bioengineering [Note A] | Female | 0.0 | 0.0 | 0.0 | 0.0 |
| | Male | 0.0 | 0.0 | 0.0 | 0.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| Eunice Kennedy Shriver National Institute of Child Health and Human Development | Female | 64.3 | 75.0 | 75.2 | 73.1 |
| | Male | 34.9 | 23.6 | 23.3 | 25.4 |
| | Other | 0.8 | 1.4 | 1.4 | 1.5 |
| National Institute on Deafness and Other Communication Disorders [Note C] | Female | 0.0 | 0.0 | 26.5 | 0.0 |
| | Male | 0.0 | 0.0 | 73.5 | 0.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Institute of Dental and Craniofacial Research | Female | 49.2 | 62.6 | 51.2 | 60.7 |
| | Male | 50.8 | 35.0 | 48.3 | 39.1 |
| | Other | 0.0 | 2.4 | 0.5 | 0.2 |
| National Institute of Diabetes and Digestive and Kidney Diseases | Female | 75.2 | 77.0 | 65.8 | 67.5 |
| | Male | 24.8 | 23.0 | 32.8 | 32.1 |
| | Other | 0.0 | 0.0 | 1.4 | 0.4 |
| National Institute on Drug Abuse | Female | 37.4 | 38.3 | 41.1 | 25.5 |
| | Male | 39.8 | 40.1 | 56.5 | 73.8 |
| | Other | 22.8 | 21.6 | 2.5 | 0.8 |
| National Institute of Environmental Health Sciences [Note E] | Female | 67.6 | 50.9 | 0.0 | 0.0 |
| | Male | 32.4 | 49.1 | 0.0 | 0.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Institute of General Medical Sciences [Note A] | Female | 0.0 | 0.0 | 0.0 | 0.0 |
| | Male | 0.0 | 0.0 | 0.0 | 0.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Institute of Mental Health | Female | 64.5 | 49.4 | 51.1 | 52.5 |
| | Male | 35.5 | 50.6 | 48.9 | 47.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.5 |
| National Institute of Minority Health and Health Disparities [Note A] | Female | 0.0 | 0.0 | 0.0 | 0.0 |
| | Male | 0.0 | 0.0 | 0.0 | 0.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| National Institute of Neurological Disorders and Stroke | Female | 38.6 | 40.0 | 39.4 | 43.5 |
| | Male | 61.4 | 60.0 | 60.6 | 56.4 |
| | Other | 0.0 | 0.0 | 0.1 | 0.0 |
| National Institute of Nursing Research [Note C] | Female | 0.0 | 47.7 | 62.8 | 83.7 |
| | Male | 0.0 | 52.3 | 37.2 | 16.3 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |

| NIH or IC | | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| National Library of Medicine [Note A] | Female | 0.0 | 0.0 | 0.0 | 0.0 |
| | Male | 0.0 | 0.0 | 0.0 | 0.0 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |
| NIH Clinical Center [Note C] | Female | 46.1 | 46.3 | 44.9 | 45.5 |
| | Male | 53.9 | 53.7 | 55.1 | 54.5 |
| | Other | 0.0 | 0.0 | 0.0 | 0.0 |

Source: NIH. | GAO-16-13

Notes: Two ICs, the Center for Information Technology and the Center for Scientific Review, do not conduct or fund any clinical research studies or phase III trials, and thus, are not included in this table. Additionally, we do not include the National Center for Research Resources in this table, as it ceased operations in fiscal year 2012, or the Office of Director and Office of Research on Women's Health, as they are not ICs and did not fund phase III clinical trials during the fiscal year 2011-2014 time period. "Other" enrollment includes participants whose sex was not reported or is otherwise unknown.

Note A: This IC did not report any enrollees in IC-funded phase III clinical trials in fiscal years 2011-2014.

Note B: This IC did not begin operations until fiscal year 2012.

Note C: These ICs enrolled fewer than 1,200 participants in each year for fiscal years 2011-2014. According to NIH, these ICs typically support very few phase III clinical trials.

Note D: There was only one individual participant enrolled in the years for which this IC reported enrollment.

Note E: According to NIH, the National Institute of Environmental Health Sciences portfolio supports very few NIH-defined phase III clinical trials. The enrollment data reported in fiscal years 2011and 2012 primarily reflects the initial recruitment of mothers and young children into a study in fiscal year 2011 and fathers and older siblings in fiscal year 2012.

# Appendix IV: Comments from the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

SEP 25 2015

Linda T. Kohn
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Kohn:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "NATIONAL INSTITUTES OF HEALTH: Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research" (GAO-16-13).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

**GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT "NATIONAL INSTITUTES OF HEALTH: BETTER OVERSIGHT NEEDED TO HELP ENSURE CONTINUED PROGRESS INCLUDING WOMEN IN HEALTH RESEARCH" (GAO-16-13)**

The National Institutes of Health (NIH) appreciates the review conducted by GAO and the opportunity to provide clarifications on this draft report. The NIH concurs with the GAO recommendations and respectfully submits the following general comments as well as specific responses to each recommendation.

The NIH takes the responsibility of ensuring the appropriate inclusion of women (and other groups) in clinical research and clinical trials very seriously. This report focuses on examination of clinical trials, which are a subset of clinical research; however, the NIH is committed to considering inclusion in all clinical research which, as the NIH defines it, encompasses almost all research considered human subjects' research. For context, it is important to note that the clinical trials the NIH funds are part of a much larger effort with funding for trials also coming from other federal agencies, public or private research organizations, and industry. For example, in 2014, out of the 23,304 clinical trials first received into ClinicalTrials.gov, only 1,314 were attributed to the NIH as the funder. Other stakeholders also play important roles in the "inclusion enterprise" such as the other funders of trials, the Food and Drug Administration (FDA), and the journals that publish results. Some of the conclusions and supporting statements in this report incorporate challenges observed in the broader trial efforts in terms of representation of women and reporting of findings by sex. The NIH believes these are valid perspectives to incorporate into this report in terms of understanding the challenges the entire clinical research enterprise faces in ensuring the appropriate inclusion of women in clinical trials; yet it is also important to consider this context in terms of what the NIH can specifically address. The NIH embraces continuing to serve as a catalyst, through our clinical trials, for furthering efforts to ensure appropriate inclusion in the broader clinical trials enterprise.

The appropriate inclusion of women (and other groups) is essential to the conduct of sound research. As noted in the GAO report, the NIH has a long-standing policy addressing this issue that involves many stakeholders including applicants, peer review panels, awardees, many different NIH staff including offices within the Office of the Director as well as Institute/Center (IC) staff, IC Advisory Councils, IC and NIH leadership as well as health advocates, members of Congress, and the public. The background and rationale provided by GAO for some of the recommendations does not completely reflect the extensive process for oversight that the NIH has in place, particularly the efforts the NIH has made over the past several years to internally examine and improve its processes. However, their recommendations reinforce the extensive discussions and directions that the NIH has been considering for some time. The NIH accepts these recommendations and would like to take the opportunity to expand on what GAO describes to provide additional, relevant information in regards to te NIH's efforts in this area and to provide context to the current environment in which these recommendations will be implemented.

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restructured the inclusion governance group from a free-standing committee to a committee of senior NIH and IC staff and a trans-NIH workgroup which are better integrated with the overall NIH internal governance structure. As noted in the GAO report, it is currently co-chaired by the NIH Associate Director for Women's Health and one of the IC Directors. The NIH released a new data system (known as the Inclusion Management System) to grantees and NIH staff in October 2014. Functionality continues to be added to this data system on a regular basis some of which will be elaborated on in addressing the specific recommendations. The major goals for the Inclusion Re-Engineering Project and the Inclusion Management System included enhancing scientific oversight, automating the NIH's receipt of enrollment information, and providing more transparency between awardees and staff regarding inclusion information.

Additional goals for the Inclusion Re-Engineering Project also focus on different ways to understand inclusion in our research portfolio. When the NIH developed its first enrollment data system, the systems and processes didn't exist to easily examine inclusion information with scientific information on awards. Examining representation at the NIH aggregate level provides a high level "barometer" of overall inclusion efforts, and knowing that we typically have representation of women at approximately 50% or higher in clinical research and the NIH-defined Phase III trials is encouraging. However, another goal is to develop methods to better understand inclusion in specific scientific areas across the NIH. Some ICs already conduct specific portfolio analyses on an *ad-hoc* basis to understand the representation of women in studies of certain diseases, but these efforts are typically manual and can be resource-intensive. More recently developed tools related to scientific analysis and reporting will facilitate efforts in this area and allow the NIH to more readily understand where potential gaps in its funding portfolio may exist.

Other recent activities at the NIH also interplay with oversight of inclusion policy, and the NIH is poised to build on these opportunities to further enhance its mission and ensure appropriate inclusion. The NIH recently announced new policies to enhance the rigor and reproducibility[1,2] of the research it supports. An important aspect of this effort is consideration of sex as biological variable[3] in both vertebrate animal and human studies. This new policy will expand consideration of sex across the research continuum from preclinical studies to informing clinical interventions, and these efforts complement existing NIH inclusion policy. The NIH is also currently examining its clinical trials policies and procedures. The NIH requested public comment on a draft policy[4] regarding the dissemination of funded clinical trial information and is in the process of analyzing that feedback. As the clinical trials policy discussion evolves, there will be opportunities to consider how oversight of inclusion and reporting of results for females and males (sex-specific results) can be folded into those discussions as well.

A key concern for GAO is that the NIH inclusion policy is inconsistent with federal internal control standards because we do not identify and report the number of NIH-defined Phase III clinical trials that conduct sex-differences analyses or widely disseminate IC-level enrollment data. A cornerstone of the NIH system is its peer review process, which involves recruiting scientific experts from the relevant field(s) to review each research application or proposal to the NIH including inclusion plans. The NIH provides explicit guidance to applicants, peer reviewers, and staff about expectations for the consideration of inclusion in the design of all clinical research as well as analysis expectations specific to NIH-defined

[1] http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-103.html
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[4] http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html

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Phase III trials. Peer review is a critical part of inclusion oversight because it considers each trial individually to ensure that the design and inclusion strategies are appropriate for that given study. The NIH business process for peer review is documented, communicated, and monitored. The NIH also reports biennially regarding the proportion of applications NIH peer review panels found to be unacceptable for their inclusion plans. An unacceptable inclusion plan constitutes a bar to funding that must be resolved by the NIH staff before an award can be issued. While the NIH believes that the peer review process aligns with GAO's internal control standards, we also recognize that there may be additional measures the NIH can take to further its oversight of analysis and reporting of sex-specific results, which we discuss further with the recommendations; however, there are also concerns regarding some potential limitations to Recommendations 4 and 5 that will need to be carefully considered. In terms of internal control standards and sharing of IC-level enrollment data, each IC Biennial Report on Inclusion is shared with the IC's Advisory Council, which is a key group for achieving external stakeholder input and whose meetings are open to the public. The IC Advisory Council review is another explicit control process that is clearly recorded and documented as well. However, the NIH does recognize that in terms of information sharing, there are limitations to this current approach, which we address more fully in the response to Recommendation #1.

In addition to the critical role of peer reviewers in assessing proposed inclusion plans, the program officer (PO) at the NIH also serves an important role in the management and oversight of the research project once an award is made. This includes monitoring of inclusion as part of the scientific progress of active research awards. The NIH acknowledges that examining summary information about inclusion is an important lens with which to view how women are included in our research portfolio. However, at the same time, because of the breadth and diversity of the NIH's research mission, the individual award level assessment and oversight provided by peer reviewers and POs also plays a critical part in assuring that women are appropriately represented in a given clinical trial in a particular disease or condition. While the GAO references the PO role in the report, much of the emphasis in the recommendations is placed on more aggregated views of assessing compliance. The concerns the GAO raises are valid; however, the NIH also stresses that the PO is essential to the monitoring process to ensure the appropriate inclusion of women as part of the scientific oversight of each clinical trial. Many NIH-defined Phase III clinical trials are awarded in a manner that requires substantial involvement by the NIH staff. The NIH staff often review and approve statistical analysis plans that would include analysis of potential sex differences. There are also other "partners" involved in the management of these clinical trials such as an independent data and safety monitoring board (DSMB) that will comment on the plans and provide feedback to the IC on a regular basis. Inclusion oversight is complex and needs to be examined from different levels ranging from the individual trial (or even recruitment site) level through aggregations by disease/condition, IC, and NIH levels. The NIH recognizes that none alone will suffice in understanding this important issue but also stresses the importance of the NIH staff in the process.

In summary, the NIH accepts these recommendations because the NIH shares GAO's overarching concerns about inclusion. The information provided above supports our commitment to the inclusion policy and its oversight and provides context for our specific responses to each recommendation. The NIH welcomes the role of serving as a catalyst to further efforts to ensure the appropriate inclusion of women (and other groups) in the clinical trials enterprise. The NIH staff is currently engaging with colleagues at the FDA on shared concerns in the area of inclusion. In addition, while the NIH does not have purview over publication decisions, staff is actively engaging journal editors in this area.[5] The NIH

[5] http://www.ncbi.nlm.nih.gov/books/NBK84192/pdf/Bookshelf_NBK84192.pdf

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looks forward to continued, thoughtful engagement with Congress, GAO, and other stakeholders in this important area.

**GAO Recommendation 1:**
Make IC-level enrollment data readily available through public means, such as its regular biennial report to Congress on the inclusion of women in research, or through its website.

**NIH Response:**
The NIH concurs with GAO's finding and corresponding recommendation regarding making IC-level enrollment data readily available through public means.

The ICs currently provide their IC-level enrollment information during open, public sessions of their Advisory Council meetings along with a written report certifying their compliance with the NIH inclusion policy. This means that the materials are available to the public, but we also acknowledge GAO's point that they could be made more accessible. Until 2009, these IC reports were incorporated into the overall biennial report that was previously submitted on paper to Congress. In this time period, the NIH began efforts to reduce the large volume of paper associated with this and other related reports. Unfortunately, as the inclusion report began to transition to electronic submission, there has been a period of time where the IC reports did not get incorporated. The NIH recognizes that there are opportunities to increase the accessibility of these materials, particularly to the public. The NIH has already begun efforts to standardize the reporting format for the ICs as a part of the ongoing NIH Inclusion Re-Engineering Project. The NIH is also continuing efforts to standardize a minimum set of data tables and graphics for each IC to provide for biennial reports in addition to any further analyses the IC would like to provide.

**GAO Recommendation 2:**
Examine approaches for aggregating more detailed enrollment data at the disease and condition level, and report on the status of this examination to key stakeholders and through its regular biennial report to Congress on the inclusion of women in research.

**NIH Response:**
The NIH concurs with GAO's finding and corresponding recommendation regarding examining approaches for aggregating more detailed enrollment data at the disease and condition level, and reporting on the status of this examination to key stakeholders and through its regular biennial report to Congress.

It is important to note that some ICs already conduct analyses to understand the inclusion of women in trials of specific diseases and conditions.[6] They typically do this on an "as needed" basis for IC planning as well as to be responsive to external stakeholder concerns. However, this process is a more manual, time-intensive effort. One of the goals of the Inclusion Re-Engineering Project is to enhance the NIH's ability to more readily analyze inclusion information at the disease/condition level across ICs. This will streamline and standardize our efforts to better understand where gaps in representation may exist in the NIH portfolio particularly in diseases/conditions that may span multiple ICs. The Research, Condition, and Disease Categorization (RCDC) process was developed by the NIH over several years, and the first reports were released in 2009. This system allows for categorization and reporting of awards by different scientific areas. Now that the Inclusion Management System (IMS) has been deployed, the NIH is

[6] http://www.nhlbi.nih.gov/about/directorscorner/messages/womens-health-legacy-commitment-%E2%80%A6

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exploring the opportunity to understand inclusion information within specific disease and condition reporting categories. All reporting approaches come with potential limitations and by combining information from different data processes, these limitations can be compounded. However, the potential exists for these various systems to provide yet another tool for understanding inclusion in the NIH portfolio. The NIH is in the process of transitioning enrollment information from ongoing awards from our previous data system into the IMS, thus it will take some time before these opportunities can be fully considered. The NIH is taking measured steps in developing potential analyses to ensure that the limitations are minimized and that information about inclusion in different research categories provides meaningful insight into the NIH portfolio. For example, it is important to note that specific disease categories may vary with respect to the percentage of women with the disease or condition relative to the percentage of women in the population. In terms of providing this information to external stakeholders, the biennial inclusion report is one option, but there may be other, complementary approaches that can be developed as well to ensure this information is more readily available.

**GAO Recommendation 3:**
Ensure that program officers have a means of recording their monitoring of awardees plans for and progress in conducting analysis of potential sex differences.

**NIH Response:**
The NIH concurs with GAO's finding and corresponding recommendation regarding ensuring that program officers have a means of recording their monitoring of awardees plans for and progress in conducting analysis of potential sex differences.

As noted in the general summary comments, the NIH PO plays a key role in the monitoring and oversight of NIH research awards. The NIH already has tools in place to monitor scientific, fiscal, and administrative progress in ongoing awards. During the NIH Inclusion Re-Engineering Project, the NIH developed plans to streamline and better integrate its approach to programmatic oversight of inclusion, including oversight of potential sex difference analyses for NIH-defined Phase III clinical trials. Based on the results of modeling on the inclusion business process, the NIH has more oversight, particularly for Phase III trial requirements, because the NIH made IMS directly accessible through the Program Module.[7] Previously, the information about sex-differences analyses was contained in a separate process and part of the NIH data system. The timeline to implement these changes in procedures was distributed across FY15 and FY16 to ensure staff input and understanding of the changes. As of FY15 (starting October 2014), the IMS was deployed, questions in the program checklist regarding inclusion enrollment were revised, and new tools were provided to staff in monitoring enrollment. As of FY16 (starting October 2015), questions specific to the issue of sex-differences analyses will be incorporated into the program checklists used to work up new (initial) and annual (non-competing) awards.

In addition, as noted by GAO, the NIH is considering plans to require all clinical trials conducted or supported by NIH to register and report findings in ClinicalTrials.gov.[8] This has the potential to enhance NIH's oversight of reporting of potential analyses by sex. In many instances, the award from the NIH may be closed out prior to completion of analysis and/or reporting of trial results including sex

[7] The Program Module provides Program Officials (PO) access to information and documents for applications and grants in their portfolio, with the ability to execute reporting and approval transactions in real time.
[8] http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html

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**GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT "NATIONAL INSTITUTES OF HEALTH: BETTER OVERSIGHT NEEDED TO HELP ENSURE CONTINUED PROGRESS INCLUDING WOMEN IN HEALTH RESEARCH" (GAO-16-13)**

differences. If the NIH clinical trials policy moves forward, ClinicalTrials.gov may provide an opportunity to continue oversight through the completion and reporting phases of a given clinical trial.

**The NIH would like to jointly address GAO Recommendations 4 and 5 together because they involve the same topic and only separate collection and reporting of the same information.**

**GAO Recommendation 4:**
On a regular basis, systematically collect and analyze summary data regarding awardees' plans for analysis of potential sex differences, such as the proportion of trials being conducted that intend to analyze differences in outcomes for men and women.

**GAO Recommendation 5:**
Report on this summary data and analysis in its regular biennial report to Congress on the inclusion of women in research

**NIH Response:**
The NIH concurs with GAO's finding regarding the need to systematically collect, analyze, and report summary data for trials that involve sex-differences analyses.

The NIH agrees that understanding which trials involve a sex-differences analysis is a critical issue in the appropriate inclusion of women in clinical trials and ultimately ensuring that the results inform clinical practice in an appropriate manner for both males and females. However, simply collecting and reporting the number of trials that plan such analysis may not be a sufficient or particularly meaningful benchmark for this important issue. Reporting the proportion (or number) of trials implies that all trials should have an analysis. This assumption is incorrect since not all trials would be expected to have one. For example, sex differences analysis would not be expected for a trial of prostate or cervical cancer.

Also, only recording and reporting information about the proportion of the NIH funded trials that plan a sex-differences analysis may not accomplish the desired goal, which is to ensure that analyses happen, as needed, and that appropriate oversight is provided from the initial trial design and peer review through trial completion, data analysis, and results reporting. As noted in the GAO report and the NIH general summary comments above, the NIH peer review system provides the critical, first level of scrutiny to determine whether the trial design is scientifically sound and justified, including whether analysis by sex is proposed. The PO at the NIH then provides the important oversight of ongoing, individual trials to ensure that they continue to be in compliance with analysis requirements.

An alternative approach to the one recommended by GAO could be to consider collecting and reporting information about whether an analysis was proposed and ultimately conducted, unless justification is provided for not conducting those planned analyses. Because trials can change after they are initiated, NIH needs to consider the potential limitations of this concept further.

As the NIH considers additional ways we can summarize and report to stakeholders on compliance with this issue, the NIH will also strengthen its ongoing efforts in the following areas:

1) clarify instructions to applicants to ensure that they understand the need to explicitly justify whether sex-differences analyses are necessary for their proposed science;

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**GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT "NATIONAL INSTITUTES OF HEALTH: BETTER OVERSIGHT NEEDED TO HELP ENSURE CONTINUED PROGRESS INCLUDING WOMEN IN HEALTH RESEARCH" (GAO-16-13)**

2) ensure that peer reviewers understand their critical role in assessing that justification and require that they explicitly comment on this aspect of the trial design; and

3) continue to provide follow-up and oversight through program officer monitoring including consideration of potential tools to further assist POs in assessing progress.

The NIH will also take the opportunity to consider the goals of the GAO recommendations along with other, related ongoing activities at the NIH, including:

1) Consideration of Sex as a Biological Variable. The NIH's new policy on sex as a biological variable[9] will reinforce the importance of considering sex during the design and conduct of research in both animal and human studies. The plans broaden expectations for sex-specific results reporting, and the NIH is in the process of developing procedures to ensure compliance. This policy can, in some ways, be viewed as an adjunct to the inclusion of women policy, and it is logical to consider them together in developing and refining monitoring and oversight approaches to sex-specific results reporting including for NIH-defined Phase III clinical trials.

2) Clinical Trials Oversight at NIH. The NIH has initiated efforts to enhance its monitoring and oversight of clinical trials. NIH would like to take this opportunity to also consider how results reporting related to sex may be incorporated as part of these discussions.

3) Results Reporting in ClinicalTrials.gov. Because an NIH award may end prior to the timeline for trial results and reporting, the ongoing award monitoring process could be enhanced to ensure compliance with the analysis component of the inclusion policy. The award monitoring process does provide an important annual assessment of progress; however, ClinicalTrials.gov may provide an opportunity to continue oversight and ensure compliance that planned analyses are actually conducted and reported. This approach needs to be considered further.

[9] http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html

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# Appendix V: GAO Contact and Staff Acknowledgments

## GAO Contact

Linda T. Kohn, (202) 512-7114 or kohnl@gao.gov

## Acknowledgments

In addition to the contact named above, Karen Doran, Assistant Director; Amanda Cherrin; Emily Loriso; and Julie T. Stewart made key contributions to this report. Jennie F. Apter, Leia Dickerson, Krister Friday, and Jacquelyn Hamilton also contributed to the development of this report.

# Appendix VI: Accessible Data

## Accessible Text and Data Tables

**Data Tables for Figure 1: Enrollment in All National Institutes of Health (NIH) Funded Clinical Research by Sex, as a Percentage of Total Enrollment, Fiscal Years 2005-2014**

All clinical research

| Fiscal year | Female | Male | Unknown |
|---|---|---|---|
| 2005 | 60.4% | 37.8% | 1.8% |
| 2006 | 63.9% | 34.9% | 1.3% |
| 2007 | 58.2% | 39.5% | 2.3% |
| 2008 | 60.0% | 38.9% | 1.1% |
| 2009 | 59.8% | 39.6% | 0.7% |
| 2010 | 56.1% | 43.0% | 0.9% |
| 2011 | 59.4% | 39.3% | 1.3% |
| 2012 | 57.0% | 41.8% | 1.1% |
| 2013 | 56.7% | 42.1% | 1.3% |
| 2014 | 57.2% | 38.6% | 4.1% |

Phase III

| Fiscal year | Female | Male | Unknown |
|---|---|---|---|
| 2005 | 59.0% | 40.0% | 1.0% |
| 2006 | 62.9% | 36.0% | 1.1% |
| 2007 | 54.9% | 42.2% | 2.8% |
| 2008 | 57.5% | 40.3% | 2.2% |
| 2009 | 53.0% | 42.3% | 4.7% |
| 2010 | 53.0% | 43.0% | 4.0% |
| 2011 | 57.0% | 38.0% | 5.0% |
| 2012 | 62.1% | 32.7% | 5.2% |
| 2013 | 73.3% | 25.9% | 0.7% |
| 2014 | 60.0% | 39.4% | 0.6% |

Source: GAO analysis of NIH data. | GAO-16-13

# Agency Comments

## Department of Health and Human Services

**Accessible Text for Appendix IV: Comments from the Department of Health and Human Services**

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DEPARTMENT OF HEALTH & HUMAN SERVICES
OFFICE OF THE SECRETARY
Assistant Secretary for Legislation Washington, DC 20201

September 25, 2015

Linda T. Kohn
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Mr. Gomez

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "NATIONAL INSTITUTES OF HEALTH: Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research" (GAO-16-13).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,
Jim R. Esquea
Assistant Secretary for Legislation

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The National Institutes of Health (NIH) appreciates the review conducted by GAO and the opportunity to provide clarifications on this draft report. The NIH concurs ·with the GAO recommendations and respectfully

submits the following general comments as well as specific responses to each recommendation.

The NIH takes the responsibility of ensuring the appropriate inclusion of women (and other groups) in clinical research and clinical trials very seriously. This report focuses on examination of clinical trials, which are a subset of clinical research; however, the NIH is committed to considering inclusion in all clinical research which, as the NIH defines it, encompasses almost all research considered human subjects' research. For context, it is important to note that the clinical trials the NIH funds are part of a much larger effort with funding for trials also coming from other federal agencies, public or private research organizations, and industry. For example, in 2014, out of the 23,304 clinical trials first received into ClinicalTrials.gov, only 1,314 were attributed to the NIH as the funder. Other stakeholders also play important roles in the "inclusion enterprise" such as the other funders of trials, the Food and Drug Administration (FDA), and the journals that publish results. Some of the conclusions and supporting statements in this report incorporate challenges observed in the broader trial efforts in terms of representation of women and reporting of findings by sex. The NIH believes these are valid perspectives to incorporate into this report in terms of understanding the challenges the entire clinical research enterprise faces in ensuring the appropriate inclusion of women in clinical trials; yet it is also important to consider this context in terms of what the NIH can specifically address. The NIH embraces continuing to serve as a catalyst, through our clinical trials, for furthering efforts to ensure appropriate inclusion in the broader clinical trials enterprise.

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relevant information in regards to the NIH's efforts in this area and to provide context to the current environment in which these recommendations will be implemented.

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Note 1: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-103.html

Note 2: http://grants.nih.gov/reproducibility/index.htm

Note 3: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html

Note 4: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html

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Phase III trials. Peer review is a critical part of inclusion oversight because it considers each trial individually to ensure that the design and inclusion strategies are appropriate for that given study. The NIH business process for peer review is documented, communicated, and monitored. The NIH also reports biennially regarding the proportion of applications NIH peer review panels found to be unacceptable for their inclusion plans. An unacceptable inclusion plan constitutes a bar to funding that must be resolved by the NIH staff before an award can be issued. While the NIH believes that the peer review process aligns with GAO's internal control standards, we also recognize that there may be additional measures the NIH can take to further its oversight of analysis and reporting of sex-specific results, which we discuss further with the recommendations; however, there are also concerns regarding some potential limitations to Recommendations 4 and 5 that will need to be carefully considered. In terms of internal control standards and sharing of IC-level enrollment data, each IC Biennial Report on Inclusion is shared with the IC's Advisory Council, which is a key group for achieving external stakeholder input and whose meetings are open to the public. The IC Advisory Council review is another explicit control process that is clearly recorded and documented as well. However, the NIH does recognize that in terms of information sharing, there are limitations to this current approach, which we address more fully in the response to Recommendation #1.

In addition to the critical role of peer reviewers in assessing proposed inclusion plans, the program officer (PO) at the NIH also serves an important role in the management and oversight of the research project once an award is made. This includes monitoring of inclusion as part of the scientific progress of active research awards. The NIH acknowledges that examining summary information about inclusion is an important lens with which to view how women are included in our research portfolio. However, at the same time, because of the breadth and diversity of the NIH's research mission, the individual award level assessment and oversight provided by peer reviewers and POs also plays a critical part in assuring that women are appropriately represented in a given clinical trial in a particular disease or condition. While the GAO references the PO role in the report, much of the emphasis in the recommendations is placed on more aggregated views of assessing compliance. The concerns the GAO raises are valid; however, the NIH also stresses that the PO is essential to the monitoring process to ensure the appropriate inclusion of women as part of the scientific oversight of each clinical trial.

Many NIH-defined Phase III clinical trials are awarded in a manner that requires substantial involvement by the NIH staff. The NIH staff often review and approve statistical analysis plans that would include analysis of potential sex differences. There are also other "partners" involved in the management of these clinical trials such as an independent data and safety monitoring board (DSMB) that will comment on the plans and provide feedback to the IC on a regular basis. Inclusion oversight is complex and needs to be examined from different levels ranging from the individual trial (or even recruitment site) level through aggregations by disease/condition, IC, and NIH levels. The NIH recognizes that none alone will suffice in understanding this important issue but also stresses the importance of the NIH staff in the process.

In summary, the NIH accepts these recommendations because the NIH shares GAO's overarching concerns about inclusion. The information provided above supports our commitment to the inclusion policy and its oversight and provides context for our specific responses to each recommendation. The NIH welcomes the role of serving as a catalyst to further efforts to ensure the appropriate inclusion of women (and other groups) in the clinical trials enterprise. The NIH staff is currently engaging with colleagues at the FDA on shared concerns in the area of inclusion. In addition, while the NIH does not have purview over publication decisions, staff is actively engaging journal editors in this area [Note 5]. The NIH

Note 5: http://www.ncbi.nlm.nih.gov/books/NBK84192/pdf/Bookshelf_NBK84192.pdf

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looks forward to continued, thoughtful engagement with Congress, GAO, and other stakeholders in this important area.

**GAO Recommendation 1:** Make IC-level enrollment data readily available through public means, such as its regular biennial report to Congress on the inclusion of women in research, or through its website.

**NIH Response:** The NIH concurs with GAO's finding and corresponding recommendation regarding making IC-level enrollment data readily available through public means.

The ICs currently provide their JC-level enrollment information during open, public sessions of their Advisory Council meetings along with a written report certifying their compliance with the NIH inclusion policy. This means that the materials are available to the public, but we also acknowledge GAO's point that they could be made more accessible. Until 2009, these IC reports were incorporated into the overall biennial report

that was previously submitted on paper to Congress. In this time period, the NIH began efforts to reduce the large volume of paper associated with this and other related reports. Unfortunately, as the inclusion report began to transition to electronic submission, there has been a period of time where the JC reports did not get incorporated. The NIH recognizes that there are opportunities to increase the accessibility of these materials, particularly to the public. The NIH has already begun efforts to standardize the reporting format for the ICs as a part of the ongoing NIH Inclusion Re-Engineering Project. The NIH is also continuing efforts to standardize a minimum set of data tables and graphics for each IC to provide for biennial reports in addition to any further analyses the IC would like to provide.

**GAO Recommendation 2:** Examine approaches for aggregating more detailed enrollment data at the disease and condition level, and report on the status of this examination to key stakeholders and through its regular biennial report to Congress on the inclusion of women in research.

**NIH Response:** The NIH concurs with GAO's finding and corresponding recommendation regarding examining approaches for aggregating more detailed enrollment data at the disease and condition level, and reporting on the status of this examination to key stakeholders and through its regular biennial report to Congress.

It is important to note that some ICs already conduct analyses to understand the inclusion of women in trials of specific diseases and conditions [Note 6]. They typically do this on an "as needed" basis for IC planning as well as to be responsive to externa l stakeholder concerns. However, this process is a more manual, time-intensive effort. One of the goals of the Inclusion Re-Engineering Project is to enhance the NIH's ability to more readily analyze inclusion information at the disease/condition level across ICs. This will streamline and standardize our efforts to better understand where gaps in representation may exist in the NIH portfolio particularly in diseases/conditions that may span multiple ICs. The Research, Condition, and Disease Categorization (RCDC) process was developed by the NIH over several years, and the first reports were released in 2009. This system allows for categorization and reporting of awards by different scientific areas. Now that the Inclusion Management System (IMS) has been deployed, the NIH is

Note 6: http://www.nhlbi.nih.gov/about/directorscorner/messages/womens-health-legacy-commitment-%E2%80%A6

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exploring the opportunity to understand inclusion information within specific disease and condition reporting categories. All reporting approaches come with potential limitations and by combining information from different data processes, these limitations can be compounded. However, the potential exists for these various systems to provide yet another tool for understanding inclusion in the NIH portfolio. The NIH is in the process of transitioning enrollment information from ongoing awards from our previous data system into the IMS, thus it will take some time before these opportunities can be fully considered. The NIH is taking measured steps in developing potential analyses to ensure that the limitations are minimized and that information about inclusion in different research categories provides meaningful insight into the NIH portfolio. For example, it is important to note that specific disease categories may vary with respect to the percentage of women with the disease or condition relative to the percentage of women in the population. In terms of providing this information to external stakeholders, the biennial inclusion report is one option, but there may be other, complementary approaches that can be developed as well to ensure this information is more readily available.

**GAO Recommendation 3:** Ensure that program officers have a means of recording their monitoring of awardees plans for and progress in conducting analysis of potential sex differences.

**NIH Response:** The NIH concurs with GAO's finding and corresponding recommendation regarding ensuring that program officers have a means of recording their monitoring of awardees plans for and progress in conducting analysis of potential sex differences.

As noted in the general summary comments, the NIH PO plays a key role in the monitoring and oversight of NIH research awards. The NIH already has tools in place to monitor scientific, fiscal, and administrative progress in ongoing awards. During the NIH Inclusion Re-Engineering Project, the NIH developed plans to streamline and better integrate its approach to programmatic oversight of inclusion, including oversight of potential sex difference analyses for NIH-defined Phase III clinical trials. Based on the results of modeling on the inclusion business process, the NIH has more oversight, particularly for Phase III trial requirements, because the NIH made IMS directly accessible through the Program Module [Note 7]. Previously, the information about sex-differences analyses was contained in a separate process and part of the NIH data system. The timeline to implement these changes in procedures was distributed across FY15 and FY16 to ensure staff input and understanding of the changes. As of FY15

(starting October 2014), the IMS was deployed, questions in the program checklist regarding inclusion enrollment were revised, and new tools were provided to staff in monitoring enrollment. As of FY16 (starting October 2015), questions specific to the issue of sex-differences analyses will be incorporated into the program checklists used to work up new (initial) and annual (non-competing) awards.

In addition, as noted by GAO, the NIH is considering plans to require all clinical trials conducted or supported by NIH to register and report findings in ClinicalTrials.gov [Note 8]. This has the potential to enhance NIH's oversight of reporting of potential analyses by sex. In many instances, the award from the NIH may be closed out prior to completion of analysis and/or reporting of trial results including sex

Note 7: The Program Module provides Program Officials (PO) access to information and documents for applications and grants in their portfolio, with the ability to execute reporting and approval transactions in real time.

Note 8: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html

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differences. If the NIH clinical trials policy moves forward, ClinicalTrials.gov may provide an opportunity to continue oversight through the completion and reporting phases of a given clinical trial.

**The NIH would like to jointly address GAO Recommendations 4 and 5 together because they involve the same topic and only separate collection and reporting of the same information.**

**GAO Recommendation 4:** On a regular basis, systematically collect and analyze summary data regarding awardees' plans for analysis of potential sex differences, such as the proportion of trials being conducted that intend to analyze differences in outcomes for men and women.

**GAO Recommendation 5:** Report on this summary data and analysis in its regular biennial report to Congress on the inclusion of women in research

**NIH Response:** The NIH concurs with GAO's finding regarding the need to systematically collect, analyze, and report summary data for trials that involve sex-differences analyses.

The NIH agrees that understanding which trial s involve a sex-differences analysis is a critical issue in the appropriate inclusion of women in clinical trials and ultimately ensuring that the results inform clinical practice in an appropriate manner for both males and females. However, simply

collecting and reporting the number of trials that plan such analysis may not be a sufficient or particularly meaningful benchmark for this important issue. Reporting the proportion (or number) of trial s implies that all trials should have an analysis. This assumption is incorrect since not all trial s would be expected to have one. For example, sex differences analysis would not be expected for a trial of prostate or cervical cancer.

Also, only recording and reporting information about the proportion of the NIH funded trials that plan a sex-differences analysis may not accomplish the desired goa l, which is to ensure that analyses happen, as needed, and that appropriate oversight is provided from the initial trial design and peer review through trial completion , data analysis, and results repo1ting. As noted in the GAO report and the NIH general summary comments above, the NIH peer review system provides the critical, first level of scrutiny to determine whether the trial design is scientifically sound and justified, including whether analysis by sex is proposed. The PO at the NIH then provides the important oversight of ongoing, individual trials to ensure that they continue to be in compliance with analysis requirements.

An alternative approach to the one recommended by GAO could be to consider collecting and reporting information about whether an analysis was proposed and ultimately conducted, unless justification is provided for not conducting those planned analyses. Because trials can change after they are initiated, NIH needs to consider the potential limitation s of this concept further.

As the NIH considers additional ways we can summarize and report to stakeholders on compliance with this issue, the NIH will also strengthen its ongoing efforts in the following areas:

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1. clarify instructions to applicants to ensure that they understand the need to explicitly justify whether sex-differences analyses are necessary for their proposed science;
2. ensure that peer reviewers understand their critical role in assessing that justification and require that they explicitly comment on this aspect of the trial design ; and
3. continue to provide follow-up and oversight through program officer monitoring including consideration of potential tool s to further assist POs in assessing progress.

The NIH will also take the opportunity to consider the goals of the GAO recommendations along with other, related ongoing activities at the NIH, including:

1. Consideration of Sex as a Biological Variable. The NIH's new policy on sex as a biological variable [Note 9] will reinforce the importance of considering sex during the design and conduct of research in both animal and human studies. The plans broaden expectations for sex-specific results reporting, and the NIH is in the process of developing procedures to ensure compliance. This policy can, in some ways, be viewed as an adjunct to the inclusion of women pol icy, and it is logical to consider them together in developing and refining monitoring and oversight approaches to sex-specific results reporting including for NIH-defined Phase III clinical trials.
2. Clinical Trials Oversight at NIH. The NIH has initiated efforts to enhance its monitoring and oversight of clinical trials. NIH would like to take this opportunity to also consider how results reporting related to sex may be incorporated as part of these discussions.
3. Results Reporting in ClinicalTrials.gov. Because an NIH award may end prior to the timeline for trial results and reporting, the ongoing award monitoring process could be enhanced to ensure compliance with the analysis component of the inclusion policy. The award monitoring process does provide an important annual assessment of progress; however, ClinicalTrials.gov may provide an opportunity to continue oversight and ensure compliance that planned analyses are actually conducted and reported. This approach needs to be considered further.

Note 9: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html