

National Institutes of Health

MONITORING ADHERENCE TO THE NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH

Comprehensive Report
(Fiscal Year 1997 & 1998 Tracking Data)

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Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

Background

The establishment and implementation of policies for the inclusion of women and minorities in clinical research funded by the National Institutes of Health (NIH) has its origins in the women's health movement. Following the issuance of the report of the Public Health Service Task Force on Women's Health in 1985, the NIH established a policy in 1986 for the inclusion of women in clinical research. This policy, which *urged* the inclusion of women, was first published in the NIH Guide to Grants and Contracts in 1987. Later that year, minority and other scientists at the NIH recognized the need to address the inclusion of minority populations. Therefore, in a later 1987 version of the NIH guide, a policy *encouraging* the inclusion of minorities in clinical studies was first published.

In July 1989, an *NIH Memorandum on Inclusion* stated that research solicitations should encourage inclusion of women and minorities and require a rationale if excluded, and that executive secretaries of scientific review groups should ensure that responsiveness to policy would be addressed and indicated in summary statements. In 1990, the *Congressional Caucus for Women's Issues* requested the U.S. General Accounting Office (GAO) to conduct an investigation into the implementation of the guidelines for the inclusion of women by NIH. This report, in Congressional testimony, indicated that the implementation of the policy for the inclusion of women was slow, not well communicated, that gender analysis was not implemented, and that the impact of this policy could not be determined. The GAO testimony also indicated that there were differences in the implementation of the policy recommending the inclusion of minorities, and that not all Institutes and Centers (ICs) factored adherence to these policies into the scientific merit review.

In order to ensure the policies for inclusion were firmly implemented by NIH, the Congress made what had previously been policy into Public Law, through a section in the NIH Revitalization Act of 1993 (PL 103-43)¹, entitled *Women and Minorities as Subjects in Clinical Research*. In 1994, the NIH revised its inclusion policy to meet this mandate that women and minorities must be included in all of its clinical research studies. The Revitalization Act essentially reinforced the existing NIH policies, but with four major differences:

- * that NIH ensure that women and minorities and their subpopulations be included in all human subject research;
- * that women and minorities and their subpopulations be included in Phase III clinical trials in numbers adequate to allow for valid analyses of differences in intervention effect;
- * that cost is not allowed as an acceptable reason for excluding these groups; and,
- * that NIH initiate programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as volunteers in clinical studies.

Revised inclusion guidelines developed in response to this law were published in the *Federal Register*² in March 1994, and they became effective in September 1994. The result was that NIH would not fund any grant, cooperative agreement or contract or support any intramural project to be conducted or funded in Fiscal Year 1995 and thereafter which did not comply with this policy. Research awards covered by this policy required the grantee to report annually on enrollment of women and men, and on the race and ethnicity of research participants.

Strategies to ensure that the implementation of these revised guidelines was uniform across the NIH were developed through the establishment and deliberations of an NIH Tracking and Inclusion Committee made up of representatives of the directors of each of the ICs. This trans-NIH committee, convened by the Office of Research on Women's Health (ORWH) and co-chaired with a senior IC official, meets on a regular basis, focusing on consistent and widespread adherence to the NIH guidelines by all the ICs. Working in collaboration with the Office of Extramural Research (OER), the Office of Intramural Research (OIR), and other components of the NIH, the ORWH coordinates the activity of developing and establishing data collection and reporting

methodologies to ensure uniform standards and definitions in the reporting of data on the participation of women and minority volunteers in NIH-funded research.

To ensure universal adherence to the revised inclusion guidelines, in 1994, NIH conducted extensive training on the revised inclusion guidelines for more than 1,000 NIH staff members with review, program, grants management, and/or contract management responsibilities. NIH staff, in turn, explained the requirements to applicants, reviewers, and other members of the research community. NIH staff members, reviewers, and applicants received written guidance about the requirements. This guidance outlined in great detail the circumstances under which it may be acceptable to use study populations deficient in women or minority participants, pointing out that the justification must be compelling and the scientific objectives of the research must be maintained. Training was especially important in response to 1990 GAO findings that an earlier policy was inconsistently applied and had not been well communicated or understood within the NIH or in the research community.

A variety of outreach activities were initiated to explain the revised policy to the scientific research community and to clear up common misunderstandings about the new requirements. Recognizing the importance of both recruitment and retention of human subject volunteers, NIH issued an outreach notebook, entitled *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research*, that outlines elements of outreach processes, offers practical suggestions, and provides references to additional sources of information. This outreach notebook also includes the full text of the 1994 implementation guidelines as well as a questions and answers document to provide more detailed policy guidance and some of the more commonly asked questions. The ORWH also has available a full report of its workshop on Recruitment and Retention of Women in Clinical Studies."

In June 1994, the ORWH convened a meeting of Institutional Review Board (IRB) chairs to discuss their role in implementing the revised policy. In 1996, ORWH reconvened these IRB chairs, along with representative members of the ORWH Recruitment and Retention Task Force, other experts, and representatives from NIH ICs, to discuss their experiences in implementing the 1994 guidelines. In these meetings, investigators expressed a number of lingering concerns, most notably whether it was realistic for the law to declare that cost is not a factor in designing clinical studies. Participants also raised questions about inclusion of women of childbearing potential, liability in clinical trials, and barriers to the recruitment of minority subjects. Other participants, however, noted that their worst fears about the 1994 guidelines did not materialize, in part because NIH focused on scientific considerations when developing its policy. They reported improved collaboration among institutions and emphasized the continued need for better outreach and for sharing information about effective recruitment strategies. Many noted the importance of considering community concerns, particularly those of minority populations who may feel that they are not included in enough research studies or who do not receive research results after participating in studies.

NIH's administrative procedures allow consideration of applications through a peer-review system. During initial peer review, the Scientific Review Group (SRG) evaluates the proposed enrollment of each project involving human subjects and determines whether the plan to include women and minority subjects is scientifically acceptable. An application may be judged to be unacceptable if it: 1) fails to provide sufficient information about target enrollment; 2) does not adequately justify limited or lack of inclusion of women or minorities; or 3) does not realistically address recruitment and retention. For NIH-defined Phase III clinical trials, the SRG also evaluates the description of plans to conduct analyses, as appropriate, to address differences in the intervention effect by sex/gender and/or racial/ethnic groups. Applications with unacceptable inclusion plans receive an unacceptable gender or minority code, resulting in a bar-to-funding. Such clinical research studies cannot be funded until NIH staff is assured of compliance from the investigators. This may involve requiring changes related to study design. Sometimes applicants are able to remedy the deficiencies found during initial review by providing additional information about the intended enrollment demographics.

NIH has monitored aggregate demographic data for study populations through the existing NIH computerized tracking system since Fiscal Year 1994 and tracking the inclusion of women and minorities in clinical trials has been implemented in all ICs. The NIH Tracking and Inclusion Committee continues to work on ways to refine and improve data collection methods and the quality of the data entered by each IC into this system. Aggregate data is reported annually by Fiscal Year (FY) and the most recent report available is for FY1998. Appendix A contains Tables 1 to 8 that provide aggregate enrollment data for extramural and intramural research protocols funded in FY1997 and FY1998.

Current Activities

Following a Congressional request for an assessment of NIH's progress in implementing the 1994 guidelines on including women in clinical research, the GAO issued a report in May, 2000, entitled *Women's Health - NIH Has Increased Its Efforts to Include Women in Research*³. The conclusions of this report showed that in the past decade NIH made significant progress in implementing a strengthened policy on including women in clinical research and highlighted several examples, including:

- * NIH issued guidelines to implement the 1993 NIH Revitalization Act and conducted extensive training for scientists and reviewers;
- * the review process for extramural research treats the inclusion of women and minorities as a matter of scientific merit, affecting a proposal's eligibility for funding;
- * the intramural research program now implements the inclusion policy;
- * NIH maintains a centralized inclusion tracking data system which serves as a tool for monitoring the implementation of the inclusion policy; and
- * in fiscal year 1997, more than 62% of participants in NIH-funded clinical research studies were women; minority women were also well represented, however, the proportion of Hispanic women enrolled was below their proportion in the general population.

The GAO report also included two specific recommendations to the Director of NIH to ensure the following:

- * that the requirement be implemented that Phase III clinical trials be designed and carried out to allow for the valid analysis of differences between women and men and communicate this requirement to applicants as well as requiring peer review groups to determine whether each proposed Phase III clinical trial is required to have such a study design, and that summary statements document the decision of the initial reviewers; and
- * that the NIH staff who transmit data to the inclusion tracking data system receive ongoing training on the requirements and purpose of the system.

Immediately following the release of this report, an *NIH Subcommittee Reviewing Inclusion Issues* was formed, comprised of representatives from several ICs, ORWH, OER, and OIR to reexamine NIH's system for tracking data on the inclusion of women and minorities in clinical research, recommend any necessary changes to improve the accuracy and performance of the system and reiterate the NIH policy. Four actions resulted to clarify the requirement for NIH-defined Phase III clinical trials to include women and minority groups, if scientifically appropriate, and for analysis of sex/gender and/or racial/ethnic differences to be planned and conducted by investigators engaged in NIH-funded research. These included:

- * On August 2, 2000, an NIH Guide Notice was posted on the Internet and a link is available from a new web page, *Inclusion of Women and Minorities Policy Implementation* at: http://grants.nih.gov/grants/funding/women_min/women_min.htm. This restated that NIH-defined Phase III clinical trials must be designed and conducted in a manner sufficient to allow for a valid analysis of whether the variables being studied affected women or members of minority groups differently than other subjects.
- * A new term and condition of award statement was developed and approved on August 2, 2000 to be applied to awards made after October 1, 2000 that have NIH-defined Phase III clinical trials. This statement indicates that a description of plans to conduct analyses, as appropriate, by sex/gender and/or racial/ethnic groups must be included in clinical trial protocols and the results

- of subset analyses must be reported to NIH in Progress Reports, Competitive Renewal Applications (or Contract Renewals/Extensions) and in the required Final Progress Report.
- * Effective October 1, 2000, language will be incorporated in the NIH solicitations for grant applications and contract proposals [Program Announcements (PAs), Request for Applications (RFAs), and Request for Proposals (RFPs)] stating the requirements for NIH-defined Phase III clinical trials. This clarifies the requirements that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable, and b) all investigators must report accrual, and conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.
 - * Guidelines and instructions for reviewers and Scientific Review Administrators (SRAs) are being developed to emphasize and clarify the need to review research proposals that are classified as NIH-defined Phase III clinical trials for both inclusion requirements and issues related to analyses by sex/gender and/or race/ethnicity. Instructions are being developed for the proper documentation to include in summary statements to address adherence to these policies.

Following completion of the updated guidelines and instructions, training to ensure compliance with this policy will be provided to NIH program and review officials, grants and contracts management staff and current and prospective research investigators. This training will be through workshops for NIH staff as well as for the extramural community, presentations at professional meetings and advisory committees, web-site didactic instructions and on line question and answer fact sheets. Program Officials will monitor, verify and document at the time of an award that policy requirements, including sex/gender analysis, are met and, when annual progress reports are submitted, they will determine and document whether there is continuing compliance with these policy requirements. Review Officials will introduce and discuss with reviewers the Guidelines/Instructions for reviewing Phase III clinical trials and the requirements for sufficient sample size to conduct valid analyses by sex/gender. When new and continuing applications are deficient in meeting the policy requirements, grants management and program officials will withhold funding until the Principal Investigator (PI) has satisfactorily addressed the policy requirements.

The *NIH Subcommittee Reviewing Inclusion Issues* also collected comments on the tracking system used prior to 2000 and identified issues relating to data entry, including quality control and the mechanisms of data entry. Improvements were recommended for the computerized information system, resulting in NIH undertaking the development of a new electronic database for grant review, management and administration, which will include a computerized system for standardizing and collecting inclusion data. NIH is currently developing and implementing this system. It is anticipated that the launch of the new system, together with staff training, will occur by the end of calendar year 2000.

These actions to document the requirement for inclusion, including valid analysis of sex/gender and/or race/ethnicity differences in NIH-defined Phase III clinical trials, are being implemented to respond to recommendations made in the May, 2000 GAO report. A new computer system for tracking inclusion data will also facilitate consistency in data collection and appropriate training for staff who enter data will occur following its development.

References

1. Public Law 103-43. National Institutes of Health Revitalization Act of 1993. 42 USC 289 (a)(1).
2. NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 14508 (1994).
3. *Women s Health: NIH Has Increased Its Efforts to Include Women in Research* (GAO/HEHS-00-96, May, 2000).

Appendix A

Aggregate Enrollment Data for Extramural and Intramural Research Protocols
Funded by NIH in Fiscal Year 1997 and Fiscal Year 1998

**Table 1 (1997). Aggregate Enrollment Data for All Extramural Research Protocols
Funded in FY1997**

	American Indians and Alaska Natives		Asian and Pacific Islanders		Black - Not Hispanic		Hispanic		White - Not Hispanic		Other and Unknown		Total	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Female	42,502	1.1%	577,432	15.4%	647,444	17.2%	290,735	7.7%	1,980,881	52.7%	220,332	5.9%	3,759,326	61.9%
Male	28,072	2.9%	292,246	12.9%	384,330	17.0%	195,618	8.7%	1,212,955	53.7%	144,418	6.4%	2,257,639	37.1%
Unknown	432	0.7%	1,185	1.9%	3,533	5.8%	3,945	6.5%	20,157	33.0%	31,882	52.2%	61,134	1.0%
Total	71,006	1.6%	870,863	14.3%	1,035,307	17.0%	490,298	8.1%	3,213,993	52.9%	396,632	6.5%	6,078,099	100.0%
Number of Protocols: 6,799														

**Table 2 (1998). Aggregate Enrollment Data for All Extramural Research Protocols
Funded in FY1998**

	American Indians and Alaska Natives		Asian and Pacific Islanders		Black - Not Hispanic		Hispanic		White - Not Hispanic		Other and Unknown		Total	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Female	29,959	0.7%	803,076	18.5%	660,702	15.2%	298,867	6.9%	2,330,017	53.7%	216,288	5.0%	4,338,909	67.0%
Male	24,081	1.2%	192,455	9.2%	341,128	16.4%	191,350	9.2%	1,210,602	58.1%	124,463	6.0%	2,084,079	32.2%
Unknown	1,620	2.8%	7,470	13.0%	2,176	3.8%	14,909	25.9%	10,092	17.5%	21,350	37.1%	57,617	0.9%
Total	55,660	0.9%	1,003,001	15.5%	1,004,006	15.5%	505,126	7.8%	3,550,711	54.8%	362,101	5.6%	6,480,605	100.0%
Number of Protocols: 6,947														

**Table 3 (1997). Aggregate Enrollment Data for Extramural Phase III Protocols
Funded in FY1997**

	American Indians and Alaska Natives		Asian and Pacific Islanders		Black - Not Hispanic		Hispanic		White - Not Hispanic		Other and Unknown		Total	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Female	2,902	1.3%	4,490	2.0%	26,402	11.6%	10,013	4.4%	181,603	79.5%	3,007	1.3%	228,417	74.8%
Male	2,127	2.9%	834	1.1%	16,256	21.9%	6,423	8.6%	47,829	64.3%	920	1.2%	74,389	24.3%
Unknown	1	0.0%	0	0.0%	147	5.4%	4	0.1%	102	3.8%	2,451	90.6%	2,705	0.9%
Total	5,030	1.6%	5,324	1.7%	42,805	14.0%	16,440	5.4%	229,534	75.1%	6,378	2.1%	305,511	100.0%
Number of Protocols : 320														

**Table 4 (1998). Aggregate Enrollment Data for Extramural Phase III Protocols
Funded in FY1998**

	American Indians and Alaska Natives		Asian and Pacific Islanders		Black - Not Hispanic		Hispanic		White - Not Hispanic		Other and Unknown		Total	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Female	2,195	0.6%	11,796	3.5%	50,052	14.7%	24,008	7.1%	235,271	69.3%	16,211	4.8%	339,533	67.2%
Male	1,480	0.9%	8,477	5.2%	26,456	16.1%	16,291	9.9%	100,802	61.5%	10,444	6.4%	163,950	32.5%
Unknown	10	0.7%	3	0.2%	413	28.6%	268	18.5%	630	43.6%	122	8.4%	1,446	0.3%
Total	3,685	0.7%	20,276	4.0%	76,921	15.2%	40,567	8.0%	336,703	66.7%	26,777	5.3%	504,929	100.0%
Number of Protocols : 578														

**Table 5 (1997). Aggregate Enrollment Data for Intramural Research Protocols
Conducted at the Warren G. Magnuson Clinical Center Funded in FY1997**

	American Indians and Alaska Natives		Asian and Pacific Islanders		Black - Not Hispanic		Hispanic		White - Not Hispanic		Other and Unknown		Total	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Female	8	0.1%	309	4.3%	887	12.4%	257	3.6%	5,578	78.2%	97	1.4%	7,136	49.6%
Male	13	0.2%	308	4.2%	699	9.6%	207	2.9%	5,954	82.1%	73	1.0%	7,254	50.4%
Unknown	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total	21	0.1%	617	4.3%	1,586	11.0%	464	3.2%	11,532	80.1%	170	1.2%	14,390	100.0%
Number of Protocols: 642														

**Table 6 (1998). Aggregate Enrollment Data for Intramural Research Protocols
Conducted at the Warren G. Magnuson Clinical Center Funded in FY1998**

	American Indians and Alaska Natives		Asian and Pacific Islanders		Black - Not Hispanic		Hispanic		White - Not Hispanic		Other and Unknown		Total	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Female	97	0.3%	1,181	3.4%	3,941	11.5%	1,152	3.4%	27,281	79.7%	593	1.7%	34,245	49.8%
Male	95	0.3%	1,242	3.6%	3,160	9.1%	955	2.8%	28,601	82.7%	515	1.5%	34,568	50.2%
Unknown	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total	192	0.3%	2,423	3.5%	7,101	10.3%	2,107	3.1%	55,882	81.2%	1,108	1.6%	68,813	100.0%
Number of Protocols: 1,093														

**Table 7 (1997). Aggregate Enrollment Data for Intramural Research Protocols
Conducted Off-Site in FY 1997**

	American Indians and Alaska Natives		Asian and Pacific Islanders		Black - Not Hispanic		Hispanic		White - Not Hispanic		Other and Unknown		Total	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Female	1,579	0.33%	186,222	38.82%	29,354	6.12%	5,737	1.20%	248,139	51.73%	8,637	1.80%	479,668	48.64%
Male	1,508	0.33%	178,514	39.50%	15,343	3.39%	6,527	1.44%	239,614	53.01%	10,481	2.32%	451,987	45.84%
Unknown	11,843	21.76%	814	1.50%	14,628	26.87%	1,431	2.63%	481	0.88%	25,235	46.36%	54,432	5.52%
Total	14,930	1.51%	365,550	37.07%	59,325	6.02%	13,695	1.39%	488,234	49.51%	44,353	4.50%	986,087	100.00%
Number of Protocols: 161														

**Table 8 (1998). Aggregate Enrollment Data for Intramural Research Protocols
Conducted Off-Site and Funded in FY1998**

	American Indians and Alaska Natives		Asian and Pacific Islanders		Black - Not Hispanic		Hispanic		White - Not Hispanic		Other and Unknown		Total	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Female	8,194	1.1%	231,562	32.1%	37,547	5.2%	8,819	1.2%	413,164	57.3%	22,102	3.1%	721,388	50.9%
Male	7,333	1.3%	191,397	32.7%	30,460	5.2%	9,959	1.7%	332,807	56.9%	12,700	2.2%	584,656	41.2%
Unknown	12	0.0%	73	0.1%	339	0.3%	84	0.1%	104,844	93.4%	6,894	6.1%	112,246	7.9%
Total	15,539	1.1%	423,032	29.8%	68,346	4.8%	18,862	1.3%	850,815	60.0%	41,696	2.9%	1,418,290	100.0%
Number of Protocols: 243														