

# **NIH RESPONSE TO SOCIETY FOR WOMEN'S HEALTH RESEARCH (SWHR) REPORT**

## **Introduction**

The National Institutes of Health (NIH) is dedicated to improving the health of Americans by conducting and funding medical research. The goal of the NIH is to uncover new knowledge that will help prevent, detect, diagnose, and treat disease and disability.

The institutes and centers (ICs) of the NIH have carefully reviewed the report, *National Institutes of Health: Intramural and Extramural Support for Research on Sex Differences, 2000-2003*, distributed by the Society for Women's Health Research (SWHR) on May 10, 2005. The SWHR report is based on a review of abstracts publicly available through CRISP, the NIH Computer Retrieval of Information on Scientific Projects. The NIH is committed to funding sex/gender research across all relevant scientific areas, and recognizes the SWHR's work in providing an initial, though incomplete, assessment of the status of such research.

The authors of the SWHR report draw conclusions about the level of funding from the raw count of numbers of grants as summarized in the CRISP database. The number of grants funded, however, is only one measure of research activity and scientific progress in a complex area like sex/gender research. To assess scientific progress, it is important to further examine the research portfolio of the individual ICs to determine whether key scientific questions are being answered that lead to better understanding of the biological basis of diseases such as cancer or heart diseases in women and men, the differences between them, and how that knowledge can lead to more effective prevention and treatment.

For example, the National Cancer Institute (NCI) uses such a strategy to examine its lung cancer research portfolio and to develop several high-impact, focused initiatives to reduce lung cancer mortality rates. This type of IC-specific evaluation activity would not have been identified by the SWHR review. In this particular case, the NCI Progress Review Groups identify scientific gaps and needs by using portfolio analyses and the expertise of prominent members of the research and advocacy communities. Another IC-specific example that would not be identified by the SWHR review is the recent working group on women, tobacco, and cancer led by the NCI that provides recommendations for reducing tobacco-related cancers in women. Significantly, the major recommendations of the working group highlight the need for further research to understand sex and gender differences in all aspects of the biology of tobacco-caused disease and addiction to nicotine.

This response has been prepared by the Office of Research on Women's Health (ORWH) in collaboration with the NIH institutes and centers, the Office of Extramural Research, and the Office of Intramural Research.

## **A Rich History**

Examining sex/gender differences is not a new concept for the NIH. Some of the earliest studies supported by the NIH have looked at sex/gender differences. One such example is the Framingham Heart Study that was originally funded in 1948.

Fifty-five percent of the original Framingham Heart Study cohort were women, and Framingham and other large, longitudinal epidemiologic studies continue to yield extensive information about differences between women and men in heart disease incidence, manifestations, risk factors, and prognosis.

Building on its extensive previous findings about gender differences, the National Heart, Lung, and Blood Institute (NHLBI) has placed strong emphasis on discovering and evaluating effective treatments for cardiovascular disease in women. Two recent NHLBI studies illustrate this focus, but they were conducted in all-women cohorts. Because the SWHR only reviewed studies comparing males and females, these important studies were not reflected in their report findings. The Women's Ischemia Syndrome Evaluation explored the distinctive ways in which women present with myocardial infarction or chest pain and developed diagnostic algorithms specifically for use in women. The Women's Health Study evaluated use of low-dose aspirin for primary prevention of cardiovascular disease in women. Both studies addressed major gaps in our knowledge of cardiovascular disease in women. Neither included men nor sought to address gender differences. Their purpose was to learn more about how to provide the best care for women, not only to compare women with men. The NHLBI and NIH scientists believe that this is a valid and valuable approach – and that such studies make an extremely important contribution to our ability to diagnose, treat, and prevent disease in women.

In the area of cancer research, women are actually over-represented as participants in NCI sponsored cancer treatment trials overall, and comprise 41% of patients on gender non-specific treatment trials for a 9-year period. All Phase III clinical trials sponsored by NCI include an analysis by gender for treatment effects to identify any sex differences. This is an important component of NCI-supported research into sex differences. Often no differences are detected. However, important differences have emerged, and a few examples are included below.

Recent studies of the lung cancer drug, Iressa, have revealed that women respond better to this treatment than men. A pooled analysis of data on patients with stage II and stage III colon cancer from seven randomized trials was published in the *Journal of Clinical Oncology*. It demonstrated a significant benefit for fluoruracil-based adjuvant therapy with respect to both disease-free survival (DFS) and overall survival (OS). Analysis of subsets by age, sex, and primary tumor location showed that sex was not independently prognostic for either DFS or OS; age was significant only for OS; nodal status, tumor stage, and grade were prognostic for both DFS and OS. In general, the survival outcome for childhood cancers is not significantly affected by the patient's sex. However, among children and adolescents diagnosed with acute lymphoblastic leukemia, the survival outcome for girls is known to be superior to boys, possibly related to testicular relapse. This finding has led to differences in treatment with longer treatment duration recommended for boys diagnosed with this tumor.

Another example of science being linked with gender is the research portfolio at the National Institute of Allergy and Infectious Diseases (NIAID) that focuses on a broad spectrum of

diseases and conditions disproportionately affecting women. Virtually all of NIAID's clinical trials and studies on the treatment and prevention of HIV/AIDS, autoimmune diseases, chronic fatigue syndrome, and sexually-transmitted infections (STIs) involve women.

Understanding the underlying differences in the anatomy and physiology of various biological systems, cognition, behavior, and emotion has been and continues to be an important component of the National Institute on Aging research program. That said, sexual dimorphisms do not exist in every aspect of our anatomy and physiology, but as we gain understanding of where important targets lie, hypothesis-driven analyses to compare the sexes will emerge as a natural evolution of the science.

Another example of basic science that is important to women's health and the study of sex/gender differences lies within research supported by the National Institute of General Medical Sciences (NIGMS). This institute's mission is to support the basic biological and chemical research that forms the foundation for the subsequent disease-based efforts of other NIH institutes and centers. The bulk of NIGMS support for bench research takes place in initial model systems such as yeast, fly, tissue culture cells, and rodent models. Thus, a CRISP search of NIGMS support for gender-based research would not be expected to reflect support in this area commensurate with the NIGMS budget.

NIGMS supports clinical efforts mostly in the areas of trauma and burn research and pharmacogenetics. Presently, the NIGMS Trauma and Burn Program addresses gender-based differences in patient survival and outcome. The NIGMS Pharmacogenetics Research Network (PGRN) studies diseases that disproportionately affect women (e.g., breast cancer, depression). The PGRN also incorporates women of different life stages (pre- and post-menopausal) in studies to judge the impact of estrogen status (e.g., on cardiovascular disease, possibly related to serum lipids composition). Still other studies may reveal statistically significant differences in genetic contributions to responses to drugs by sex if they occur. ORWH is participating in and co-funding the PGRN starting in July 2005. This will promote further dialogue for incorporation of important sex-based questions at the earliest stages of pharmacogenetics research studies.

Another laboratory science program not captured by the SWHR report is the rodent bioassay program for toxicity and carcinogenicity. This program, funded by the National Institute of Environmental Health Sciences (NIEHS), uses both male and female animals for comparison purposes. This ongoing, multi-million dollar effort provides data on sex differences in toxicities (e.g., immunological, reproductive, and genetic) of chemicals and other environmental agents.

The methodology used in the SWHR report also did not identify many studies of eye diseases that effect primarily women such as dry eye that are funded by the National Eye Institute (NEI). Many of these NIH studies focus on the effects of hormones on the pathophysiology of this disease. In addition, some of the grants to study eye diseases that effect men and women equally, e.g., cataract and glaucoma, include specific aims to investigate hormone-induced variations in the pathophysiology of the disease. Whereas identifying "gender differences" is not the primary aim of these studies, it would be a major outcome of any findings resulting from them, as it will be with many NIH studies.

Studies supported by the National Institute on Deafness and Other Communication Disorders (NIDCD) explore communication disorders that have a sex/gender difference, e.g. stuttering, spasmodic dysphonia, and occupational phonotrauma. Moreover, some conditions are linked to maternal infection contributing to communication disorders, e.g. cytomegalovirus being the leading cause of nonhereditary deafness. Most communication disorders other than hearing loss occur secondary to other medical conditions, e.g. a stroke (NINDS), or head and neck cancer (NCI), hence, sex/gender differences are critical when studying the diseases that caused the communication disorders rather than studying the sex/gender difference in the communication disorders themselves. This area of science is an example of where one institute leverages its research support across the NIH to maximize the gains in reducing the burden of communication disorders on the population with attention to sex/gender difference when appropriate.

International research is supported through many of the ICs, but it is the primary focus for the Fogarty International Center (FIC). In 2002, FIC launched the Stigma and Global Health Research Program in partnership with several other NIH institutes and with the ORWH. The first awards under this program were made in fiscal year 2003, and address the role of stigma in health, and how to intervene to prevent or mitigate its negative effects on the health and welfare of individuals, groups, and societies worldwide. Projects supported by this program study how stigma associated with specific health conditions interacts with individual or group characteristics (such as gender, race, religion, sexual orientation and nationality). Some projects are specifically focused on linkages between gender, stigma and health, including AIDS stigma and gender discrimination in urban Indian health care systems; culture, gender and health care stigma in Parkinson's Disease in Taiwan; and stigma, gender and risk behaviors in school youth.

Although most FIC programs do not specifically focus on sex or gender differences research, they generate significant research findings with respect to gender differences. For example, differences in HIV transmission between men and women can be attributed to many factors, some of which are anatomical and physiological and some of which are behavioral. A few studies have found higher rates of HIV transmission from mother to girl infants than boy infants, but these studies have not been able to identify if the female babies were at increased risk of transmission during pregnancy, during labor and delivery, or during breastfeeding.

Supported by the Fogarty International Research Collaboration Award (AIDS-FIRCA), a small grants program that fosters international research partnerships between NIH-supported U.S. scientists and their collaborators in the developing world on AIDS-related research, researchers at Johns Hopkins University and the University of Malawi examined the rates of HIV transmission among girl and boy infants at birth and at 6-8 weeks post delivery. Infants were enrolled in two studies to evaluate two different infant drug regimens to prevent HIV transmission. At birth, the infant girls were twice as likely as the boys to be HIV infected, indicating that the risk of infection was higher for girls during pregnancy. At 6-8 weeks of age among those infants not infected at birth, the increased risk for girls continued but it was not as strong, indicating that the risk of transmission through breastfeeding might be increased for girls too. After the researchers adjusted for the drug regimens used in the studies and other factors that might influence HIV transmission, the increased risk among infant girls still remained. Two explanations are possible. One is that infant girls are more susceptible to HIV infection before birth, due to yet to be determined genetic, immunologic, hormonal or environmental factors. The

second is that male and female infants are equally susceptible, but infected boys are more likely to die before birth than girls so the transmission among infant girls appears to be higher. These findings highlight the need for sex and gender analyses in many research studies, even when differences are not expected, if we are to better understand diseases and health conditions.

FIC, ORWH, the Canadian Institutes of Health Research and its Institute on Gender and Health, organized a *Forum on Exploring the Potential Collaborations for Sex and Gender and Global Health Research* in April 2004. Representatives from several international research funding agencies as well as 18 components of NIH discussed existing programs focused on gender and global health research as well as potential future partnerships or joint efforts in this area and identified potential areas of common activity. As a result of points raised at the meeting, FIC added new boilerplate language to all of its *NIH Guide for Grants and Contracts* notices, encouraging applicants to address not only women's health and parity issues but also to encourage applicants to consider gender dimensions of the efforts.

### **ORWH Sponsored Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health**

ORWH led the development and implementation of a new and unique program entitled, Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs). Administered by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), SCORs are designed to increase the transfer of basic research findings into clinical practice by housing laboratory and clinical studies under one roof.

Each of the centers focuses on a central theme. The SCORs are associated with one or more major medical centers. They are conducting interdisciplinary research focused on major medical problems affecting women and comparing gender contributions to health and disease. The disciplines mobilized into the SCORs are interdepartmental, intercollegiate and interinstitutional.

Eleven interdisciplinary SCORs on Sex and Gender Factors Affecting Women's Health have been funded to develop innovative approaches to advancing research on the role of sex and gender factors in health and disease. The grantees are:

**Emory University:** Pharmacology of anti-epileptic and psychotropic medications during pregnancy and lactation, Zachary Stowe, M.D.

**Medical University of South Carolina:** Role of sex and gender differences in substance abuse relapse, Kathleen Brady, M.D., Ph.D.

**Northwestern University:** Genes, androgens and intrauterine environment in polycystic ovarian syndrome (PCOS), Andrea Dunaif, M.D.

**University of California, Los Angeles:** Sex and gender factors in the pathophysiology of irritable bowel syndrome (IBS) and interstitial cystitis (IC), Emeran Mayer, M.D.

**University of California, San Francisco:** Mechanisms underlying female urinary incontinence, Jeanette Brown, M.D.

**University of Maryland:** Sex differences in pain sensitivity, Joel Greenspan, Ph.D.

**University of Michigan, Ann Arbor:** Birth, muscle injury and pelvic floor dysfunction, John DeLancey, M.D.

**University of Pittsburgh:** Genetic and environmental origins of adverse pregnancy outcomes, Gerald Schatten, Ph.D.

**University of Washington:** Mechanisms by which drug transporters alter maternal and fetal drug exposure during pregnancy, Jashvant Unadkat, Ph.D.

**Washington University:** Molecular and epidemiologic basis of acute and recurrent urinary tract infections (UTI's) in women, Scott Hultgren, Ph.D.

**Yale University:** Sex, stress and cocaine addiction, Rajita Sinha, Ph.D.

## **GENERAL METHODOLOGICAL COMMENTS ABOUT THE SWHR REPORT**

The NIH ICs have reviewed the SWHR report and offer the following nine comments about the methodology utilized by the Society.

1. **The report did not consider the vast array of funding mechanisms used across the NIH to facilitate scientific research.** For example, in focusing exclusively on grants, the report excluded contracts and cooperative agreements, which includes a number of clinical trials (e.g., U01s) and other projects that are studying sex differences. Excluding cooperative agreements from the analysis resulted in some NIH-supported clinical trials not being counted. These clinical trials recruit significant numbers of women in order to incorporate sub-group analyses on gender differences in treatment regimen and natural history of disease. These are exactly the types of studies on gender-based differences that the SWHR report authors should have wanted to recognize in their assessment, but were missed because their methodology excluded them.

Additionally, epidemiological research may not be reflected in the SWHR report since abstracts of population studies may not include key terms for subsequent subgroup analyses by sex, age, race, socioeconomic status, and other factors. These epidemiological studies are designed to assess gender differences, but they do not specifically include a hypothesis to assess gender differences, and so were also overlooked in the SWHR review. As an example, the Baltimore Longitudinal Study of Aging (BLSA), includes the study of how sex, age, and other factors, including genetics and hormones, influence changes in memory, other specific cognitive functions, and brain structure and activity. To date, these studies have revealed differences between men and women in the way the brain activates different regions in response to memory tasks and sex differences in how brain structure and brain activation patterns relate to memory performance. Yet due to the nature of these studies, none of these differences were hypothesized and so were not caught in the SWHR review of CRISP data.

Studies focused on the basic biology of a disease such as oncogenes in cancer often do not show a striking sex difference in expression and thus would not be reflected in an abstract. Where these differences do appear, they are generally pursued because they provide good clues to biological function. Endocrinology studies that look at androgens and estrogens are very prominent in the NCI-funded research. They address cancers affecting both females and males, in addition to cancers such as breast and prostate cancer.

2. **Including all grants awarded in fiscal years 2000-2003 in the denominator may be misleading, since this method includes infrastructure, basic science, and medical technology development as well as training and career development grants.** A more valid comparison would use the total number of clinical research projects for an IC as the denominator, and only look at clinical studies.
3. **The two search terms that were used, gender differences and sex differences, were restrictive enough to underestimate the number of relevant grants.** The report states that “biological differences between men and women result from a combination of factors” including genes, hormones, physiology, and the environment. But the limited search terms used in the study are not likely to retrieve a total sample of applications focused on the role of these factors in sex/gender-based biology. Grants on the effects of sex hormones on immunity, development, neuronal plasticity, cognition, sexual dimorphism, and disease susceptibility, for example, would not have been retrieved through the search. The use of terms such as *sex determination*, *sex differentiation*, *sex development*, *sex developmental disorder*, *sex hormone*, and *sexual dimorphism* would have yielded additional relevant grants.
4. **Not all scientific areas included in the report are appropriate for sex difference research.** For example, the National Institute of Child Health and Human Development (NICHD) is the lead institute in the study of women’s reproductive health, female infertility, pregnancy, fetal/maternal interactions, childbirth, and mother-to-child HIV transmission during pregnancy, childbirth and lactation, to name a few. Similarly, the NCI is the lead institute for breast, ovarian and other gynecological cancers, all of which are female-predominant or female-only conditions. These are single-sex research portfolios that specifically target women, and so strongly serve the concerns of the SWHR; but because the studies include only women without a comparison to men, they were not included in the SWHR analysis and therefore misleadingly distort the percentages of sex-relevant research at the NIH.
5. **While CRISP is a good system to use for comparison of IC-specific systems, it was not designed to be sensitive enough to capture specific nuances in scientific coding for complex scientific areas.** There is also a wide variation in the level of funding associated with different mechanisms of research support, whether it be the traditional R01 grant or one of the small grant mechanisms like an R03; so simply looking at the *number* of projects does not fully or accurately reflect the level of effort either for a given IC or for NIH as a whole. Also, the type of hypothesis-driven research that comprises the SWHR’s concern is less likely to be supported by smaller grants such as those supported by the R03 mechanism, so including this type of mechanism in the base counts may have skewed the data.
6. **Many clinical studies and clinical trials may have been excluded from the Society’s findings simply because the identification of sex-based differences was not specifically stated in the CRISP abstract, even though the study design and data collection and analysis were structured to detect such differences, as indicated in the complete grant proposal.** Since these abstracts tend to be broad overviews of a research project, they often do not reflect all the specifics of the study or of the subprojects in multi-project grants, and so an abstract-only review will underestimate research on complex topics such as sex

differences. Many studies are conducting sex/gender analysis but this may not be reflected in the specific aims of the brief abstract. Excluding titles of the abstracts/projects also serves to exclude research that focuses on sex/gender differences.

For example, the following grant titles identify NIH-funded research in two conditions in which women are over-represented – osteoporosis and osteoarthritis. These studies emphasize sex/gender, but would not be captured in the SWHR report because *sex/gender differences* does not appear in the grant abstracts: "Change in Bone, Arthritis, Function: Hormones & Obesity"; "Study of Osteoporotic Fractures"; "Idiopathic Osteoporosis in Pre-menopausal Women"; and "Bone Density and Later Bone Loss In Rural Populations". In addition, the NIAMS-supported Osteoarthritis Initiative is a major effort that includes men and women that will address sex and gender differences in the incidence and progression of osteoarthritis, and would not be included in the Society's report.

- 7. The data presented in the SWHR report are also likely to be a significant underestimate of the NIH research, since the analysis only included hypothesis-driven studies comparing males to females and excluded any studies that had only one gender.** When sufficiently powered, studies that investigate sex as a covariate provide important contributions to our knowledge base regarding sex differences in health outcomes. Once sex-based differences are identified, single-sex studies are also the most appropriate way to further investigate the “study of mechanisms and origins of sex differences” as noted in the Institute of Medicine (IOM) study and specifically cited in the SWHR report (page 7, “Discussion”). Gender-specific studies are also a driving force for important scientific discoveries on differences between males and females and should not be discounted or overlooked. For example, studies in females alone are absolutely essential for our understanding of how gonadal steroids interact with their target organs.

The very striking findings and long lasting impact of the Women's Health Initiative (WHI) appear to have been overlooked in the Society's analysis. Studies on the administration of gonadal steroids in males have been recommended by the IOM as a parallel to the WHI. Studies in females alone have clearly demonstrated that the response in women to specific pharmacological agents is often different than those of their male counterparts. Take, for example, the findings on the response of women to the common agent, aspirin, for cardiovascular outcomes. Epidemiology studies on diseases in women, such as uterine fibroids, lupus, and breast cancer are enormously important but are totally disregarded in the report's analysis.

- 8. According to the methods described in the SWHR report, one exclusion criterion is stratification of the research project measures.** If gender is only one of several factors being studied, then the study was excluded. But many factors contribute to or influence biological differences in sex/gender and are better considered together for the advancement of knowledge. One such study funded by NINDS in 2003 developed an early fMRI protocol for prediction of clinical outcome and tissue damage in acute ischemic stroke patients. The fMRI protocol will be assessed as a prognostic marker according to stroke genesis (cause) and age as well as the patient's gender.



9. The report cites that no grants were awarded by the Center for Information Technology (CIT) and the Center for Scientific Review (CSR). It should be pointed out that CIT and CSR are administrative centers, which do not issue grant awards. CIT provides leadership for all IT across the NIH, and CSR oversees all of the peer scientific review conducted throughout NIH.

## **SEX/GENDER ANALYSIS AND NIH RESEARCH**

### **A FOLLOW-UP TO THE 2000 GAO REPORT ON WOMEN'S HEALTH**

#### **What has been added to further clarify the requirement for sex/gender analysis for all NIH grants and contracts?**

Immediately following the release of the GAO report in May, 2000, entitled *Women's Health - NIH Has Increased Its Efforts to Include Women in Research*, several 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:

1. In October 2001, the **NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research and Amended Notice to the Guide for Grants and Contracts were updated and posted on the Internet with links to the ORWH home page and NIH web page, *Inclusion of Women and Minorities Policy Implementation*** at: [http://grants.nih.gov/grants/funding/women\\_min/women\\_min.htm](http://grants.nih.gov/grants/funding/women_min/women_min.htm). These documents supersede the 1994 Federal Register notice (<http://grants.nih.gov/grants/guide/notice-files/not94-100.html>) and the August 2000 notice in the NIH Guide to Grants and Contracts (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html>). These updated versions incorporate the definition of clinical research as reported in the 1997 Report of the NIH Director's Panel on Clinical research and the Office of Management and Budget (OMB) Directive 15 racial and ethnic categories to be used when reporting population data. They also provide additional guidance on reporting analyses of sex/gender and racial/ethnic differences in intervention effects for NIH-defined Phase III clinical trials (See Appendix E).
2. **An NIH Guide Notice was posted on the Internet web page, *Inclusion of Women and Minorities Policy Implementation*** at: [http://grants.nih.gov/grants/funding/women\\_min/women\\_min.htm](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 affect women or members of minority groups differently than other subjects.
3. **A new term and condition of award statement was developed and 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.

4. Effective October 1, 2000, **language was incorporated in the NIH solicitations for grant applications and contract proposals** [Program Announcements (PAs), Request for Applications (RFAs), and Request for Proposals (RFPs)] that stated the requirements for NIH-defined Phase III clinical trials clarifying 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.
5. In April 2001, **guidelines and instructions for reviewers and Scientific Review Administrators (SRAs) were 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 were developed for the proper documentation to include in summary statements to address adherence to these policies.
6. Because of concerns expressed by some that the NIH was not making sure that analyses by sex/gender were being published, and that this expressed a failure of the NIH in its compliance with the Inclusion policy/Revitalization Act, NIH undertook efforts to address this matter. **In 2001, a meeting was called of representative scientific journal editors to consider these issues,** since editorial and publication policies of journals are independent of government policies, and NIH can not dictate that sex/gender analyses must be published, while NIH can require such analyses in its own reports. **From this meeting, principles for consideration regarding publication of clinical research results were developed by an ad hoc Working Group of Representative Scientific Journal Editors of the Advisory Committee on Research on Women's Health. A statement was generated encouraging all scientific journals (1) to incorporate these principles into their editorial policy and instructions to reviewers; and (2) to publish the results or non-effects of sex/gender, race/ethnicity analysis for clinical and epidemiological studies, clearly stating the statistical limitations of analysis.** These statements were put forward with the hope that scientific journals represented at the meeting and their colleagues would consider the importance of the results of analyses by sex/gender for inclusion in future publications.

**Additional efforts to address the extramural scientific community include:**

1. **The *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research* was revised and published in the fall of 2002.** The revised Outreach Notebook, available to the research community and NIH staff, discusses the elements of Outreach, the updated NIH inclusion policy, 1997 OMB requirements for reporting race and ethnicity data, as well as information for application submission, peer review, and funding. The publication is posted on the ORWH website <http://orwh.od.nih.gov/> as well as on the NIH website for the inclusion of women and minorities policy implementation at: [http://grants1.nih.gov/grants/funding/women\\_min/women\\_min.htm](http://grants1.nih.gov/grants/funding/women_min/women_min.htm) .

2. ***A Frequently Asked Questions (FAQs) for the Inclusion, Recruitment and Retention of Women and Minority Subjects in Clinical Research*** was created as a separate document to complement the *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research*. This document provides additional guidance, in a user friendly format, regarding the revised NIH Inclusion policy and NIH requirements for sex/gender analysis. The *FAQs* file is posted on the ORWH website <http://orwh.od.nih.gov/inclusion/outreachFAQ.pdf> as well as on the NIH website for the inclusion of women and minorities policy implementation at: [http://grants1.nih.gov/grants/funding/women\\_min/women\\_min.htm](http://grants1.nih.gov/grants/funding/women_min/women_min.htm).
3. **The development and distribution of a slide show, “Sex/Gender and Minority Inclusion in NIH Clinical Research: What Investigators Need to Know!”** This presentation tool is available to assist NIH staff educating and working with the extramural community. It highlights the rationale and major components of the *NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*, as well as the 1997 OMB standards for collecting and presenting data on ethnicity and race. A copy of the presentation is included in the *Outreach Notebook for the NIH Guidelines on Women and Minorities as Subjects in Clinical Research* and is also posted on the Inclusion Page of the ORWH website [http://grants.nih.gov/grants/funding/women\\_min/training/index.htm](http://grants.nih.gov/grants/funding/women_min/training/index.htm) and the NIH website for the inclusion of women and minorities policy implementation at: [http://grants1.nih.gov/grants/funding/women\\_min/women\\_min.htm](http://grants1.nih.gov/grants/funding/women_min/women_min.htm).

**NIH includes specific language in the policy and guide notice regarding the requirement on reporting analyses of sex/gender and racial/ethnic differences in intervention effects for NIH-defined Phase III clinical trials.** As of October 2001, the amended policy applies to all grants and cooperative agreements currently active and to be awarded. Contract solicitations issued as of October 2001 must adhere to the amended policy. The Summary Statement found in the October 2001 version of the NIH Inclusion policy states that:

This notice updates the NIH policy on the inclusion of women and minorities as subjects in clinical research. It supercedes the 1994 Federal Register notice (<http://grants.nih.gov/grants/guide/notice-files/not94-100.html>) and the August 2000 notice in the NIH Guide to Grants and Contracts (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html>). It incorporates the definition of clinical research as reported in the 1997 Report of the NIH Director’s Panel on Clinical research. Also, this notice provides additional guidance on reporting analyses of sex/gender and racial/ethnic differences in intervention effects for NIH-defined Phase III clinical trials. The guidelines ensure that all NIH-funded clinical research will be carried out in a manner sufficient to elicit information about individuals of both sexes/genders and diverse racial and ethnic groups and, particularly in NIH-defined Phase III clinical trials, to examine differential effects on such groups. Since a primary aim of research is to provide scientific evidence leading to a change in health policy or standard of care, it is imperative to determine whether the intervention or therapy being studied affects women or men or members of minority groups and their subpopulations differently.

Additional language is incorporated in the amended policy clarifying the requirement for sex/gender analysis. Section IIB “**NIH-defined Phase III Clinical Trials: Planning, Conducting, and Reporting of Analyses for Sex/Gender and Race/Ethnicity Differences**” states that:

When an NIH-defined Phase III clinical trial is proposed, evidence must be reviewed to show whether or not clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected. This evidence may include, but is not limited to, data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies.

**Investigators must consider the following when planning, conducting, analyzing, and reporting an NIH-Defined Phase III clinical trial. Based on prior studies, one of the three situations below will apply:**

### **1. Prior Studies Support the Existence of Significant Differences**

If the data from prior studies strongly support the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, the primary question(s) to be addressed by the proposed NIH-defined Phase III clinical trial and the design of that trial must specifically accommodate this.

The Research Plan (for grant applications) or Proposal (for contract solicitations) must include a description of plans to conduct analyses to detect significant differences in intervention effect (see DEFINITIONS - Significant Difference) by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable. The final protocol(s) approved by the Institutional Review Board (IRB) must include these plans for analysis.

### **2. Prior Studies Support No Significant Differences**

If the data from prior studies strongly support no significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic and/or relevant subpopulation comparisons, then sex/gender and race/ethnicity will not be required as subject selection criteria. However, the inclusion and analysis of sex/gender and/or racial/ethnic subgroups is still strongly encouraged.

### **3. Prior Studies Neither Support nor Negate Significant Differences**

If the data from prior studies neither strongly support nor strongly negate the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, then the NIH-defined Phase III clinical trial will be required to include sufficient and appropriate entry of sex/gender and racial/ethnic participants, so that valid analysis of the intervention effects can be performed. However, the trial will not be required to provide high statistical power for these comparisons.

The Research Plan (for grant applications) or Proposal (for contract solicitations) must include a description of plans to conduct valid analysis (see DEFINITIONS - Valid Analysis)

by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable. The final protocol(s) approved by the Institutional Review Board (IRB) must include these plans for analysis.

Inclusion of the results of sex/gender, race/ethnicity and relevant subpopulations analyses is strongly encouraged in all publication submissions. If these analyses reveal no differences, a brief statement to that effect, indicating the groups and/or subgroups analyzed, will suffice.

For all three situations, cost is not an acceptable reason for exclusion of women and minorities from clinical trials.

The most recent comprehensive report on inclusion of women and minorities in research may be found on the ORWH website at: <http://orwh.od.nih.gov/inclusion/FinalAnnualReport2003-2004.pdf>.

## **CONCLUSION**

The NIH believes that research into sex differences and the biological basis of diseases and disorders is an important and complex area of scientific exploration, as demonstrated by the examples and assessment of the NIH research program. A more accurate measure of the NIH efforts in sex and gender research could have been captured if the CRISP analysis had included women's health as a search term. In addition, using only data from CRISP does not always provide an accurate reflection of the totality of complex scientific initiatives such as sex/gender research.

ORWH continues to lead efforts to ensure that NIH institutes and centers are in compliance with the NIH inclusion policy as legislatively mandated by the 1993 Revitalization Act and requiring that investigators engaged in NIH-funded Phase III clinical trials must plan and conduct analyses, if scientifically appropriate, on sex/gender and race/ethnicity differences. NIH-funded Phase III clinical studies must be designed and carried out in a manner sufficient to provide for valid analysis of whether the variables being studied affect women or members of minority groups differently than other subjects in the clinical study. ORWH convenes a monthly trans-NIH committee that ensures that the implementation of the inclusion policy is uniform across NIH by coordinating data collection and reporting methodologies for NIH-supported research studies.

The NIH efforts and accomplishments should not be minimized by a limited review of abstracts as reported in the CRISP database. ORWH, the Office of Extramural Research and the Office of Intramural Research are actively involved and dedicated to addressing the needs and policies for science-driven initiatives that can and will provide data on sex differences in health and disease.