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Review

Women's involvement in clinical trials: historical perspective and future implications

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ABSTRACT*

The importance of considering the differences between the male and female sex in clinical decision-making is crucial. However, it has been acknowledged in recent decades that clinical trials have not always adequately enrolled women or analyzed sex-specific differences in the data. As these deficiencies have hindered the progress of understanding women's response to medications, agencies in the United States have worked towards the inclusion of women in clinical trials and appropriate analysis of sex-specific data from clinical trials. This review outlines the history and progress of women's inclusion in clinical trials for prescription drugs and presents considerations for researchers, clinicians, and academicians on this issue.

Keywords: Clinical Trials as Topic; Patient Participation; Women's Health; Female; Research; United States

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BACKGROUND

It is important to understand the underlying variables contributing to differences between health outcomes seen in women and men. Although there are lifestyle, environmental, and behavioral differences, there are also biological differences at the molecular and cellular level.[1] These biological distinctions may contribute to the differences in clinical outcomes, which can be better understood through research.

In 2001, the Institute of Medicine published "Exploring the Biological Contributions to Human Health: Does Sex Matter?" The Committee on Understanding the Biology of Sex and Gender Differences examined biology from the cellular to the organismal and behavioral levels, and concluded that differences do occur and can have important consequences. They concluded that sex (being male or female) should be recognized as an important variable in research and increased knowledge in this area should be cultivated.[1] The growth of knowledge has become a branch of science known as sex-based biology and has led to the differentiation between the terms "sex" and "gender". "Sex" refers to the biological origin of men and women based on chromosomal differences.[1,2] It determines the physiological processes and organs of the body beyond reproductive ability.[1,2] "Gender" describes the self-representation, social, and cultural views of sex.[1,2]

Sex differences can be observed in various disease states in prevalence, diagnosis, severity, and outcomes.[2] There are disease states which disproportionally or differentially affect women. Diseases which disproportionally affect women indicate a disease burden that is greater in women than in men. Examples include breast cancer and urinary incontinence.[3] Another example is that among men and women who smoke the same number of cigarettes, women are 20% to 70% more likely to develop lung cancer.[4] Diseases may also present differently in men and women. For example, women with cardiovascular disease may experience differences in signs or symptoms.[2] Another example is sexually transmitted infections, which can affect women differently in several ways, including susceptibility, the expression of symptoms, and potential for long-term complications.[5]

In addition, there may be differences in patient outcomes or responses to treatment between men and women.[2] There are differences in the physiology of the sexes that may translate into differences in pharmacokinetics and/or pharmacodynamics for specific drugs. It is important to determine if these differences are clinically

relevant, as it may result in differences in safety or efficacy of prescription products between men and women.[6,7]

The differences between the sexes in circulating levels of endogenous hormones, such as testosterone and estradiol, can affect pharmacokinetic or pharmacodynamic parameters. Other differences seen between the sexes (e.g., weight, muscle mass, body fat, metabolic enzymes, and plasma proteins) may also impact the pharmacokinetic parameters of a particular drug.[6,8] Differences in pharmacokinetics of drugs between the sexes can be related to body composition and size.[1] Women typically have a lower body weight than men, so when taking the same dose of a drug, results in a higher level of drug.[9] Lipophilic agents may have a larger distribution in females because of their higher body fat content.[2] Other variations between the sexes include protein binding, biotransformation, and even pharmacodynamic characteristics related to receptor and enzyme levels.[1]

Pharmacodynamic differences between the sexes have been observed for particular drugs. For example, women are at increased risk of experiencing torsades de points, a potentially fatal arrhythmia, after taking drugs which prolong the QT interval.[6,7] In addition, acute liver failure as a result of certain drug exposures has also been reported in women more often than in men.[6]

Although detected pharmacokinetic and pharmacodynamics differences may not indicate clinically meaningful outcomes, there are still differences that may be clinically significant yet remain unknown.[1,9] In fact, many drugs are administered as fixed doses instead of based on weight.[10] An example of a clinically significant pharmacokinetic difference are dosing recommendations for zolpidem.[10] It was found that the same dose in women as in men caused two times the drug levels due to differences in metabolism.[10] This accounted for the potential driving impairment the morning after taking the medication.[10] In 2014, the U.S. Food and Drug Administration (FDA) initiated distinct weight-based dosing for women and men.[10] At that time, zolpidem was the only medication to have dosing based on sex.[10] This demonstrates the importance of recognizing sex as a variable that may contribute to varying responses to drugs in patients.

Health disparities are also observed between men and women, which may be due to biological, cultural, social, or economic factors.[11,12] These differences represent health outcomes that need to be addressed in order to successfully reach health equity in both sexes.[11] It has been recognized that potential differences by sex should be examined at multiple levels, from the genetic and cellular level to the organism level. In addition, potential sex differences should be studied at all lifestages. It has been recommended that sex and gender be examined as separate effects, especially when considering potential differences in diagnosis and treatment options between men and women. Women should be prospectively included and evaluated through all phases of drug development.[13]

HISTORICAL PERSPECTIVE

Opinions and actions concerning women's participation in clinical trials in the United States (U.S.) have changed through the years as governmental groups and researchers have best sought to protect the public's health, but also try to better understand how women respond to prescription drugs (Table 1).[9] Although there is recognition today of the need to include women sufficiently in clinical trials, in previous decades the consideration and inclusion of men overshadowed women in clinical research design and conduct.[2] This was observed when studying diseases prevalent in both sexes, where males, frequently of the Caucasian race, were considered to be the "norm" study population.[1,2] A type of observer bias, male bias, in assuming a male's attitude in conducting trials was another contributing factor.[2] At the same time, researchers often thought that women would have the same response as men from drugs in clinical trials.[1] They also viewed women as confounding and more expensive test subjects because of their fluctuating hormone levels.[1] Concerns of potential reproductive adverse effects led to policies and guidelines that considered pregnant women as a "vulnerable population" and, subsequently, excluded these women from research and restricted the ability of women of child-bearing potential to enroll in trials, especially in early stages of research.[1,9,14-16]

However, potential concerns and public attitudes about excluding women from important studies such as the Physicians' Health Study and the Multiple Risk Factor Intervention Trial (MRFIT) led to raised awareness of these issues.[15] A task force on women's health from the U.S. Public Health Service acknowledged in the 1980s that the quality of knowledge related to women's health was lacking due to the exclusion of women in research.[9] Government reports in the 1980s and early 1990s indicated that women were lacking representation in federally funded studies and certain diseases that affect both sexes. Examples of these diseases included heart disease and Acquired Immune Deficiency Syndrome (AIDS). Finally in 1992, a discussion about women in clinical trials lead by the FDA and the Food and Drug Law Institute concluded that in order to understand the response of women to pharmaceutical agents, young women needed to be included in clinical trials.[9]

Discussed below are the history and progress in the U.S. of inclusion of women of child-bearing potential in clinical trials for prescription drugs; the involvement of pregnant women, actions taken by groups outside of the U.S., preclinical trials, or trials for other products, such as medical devices, are outside of the scope of this review.

U.S. Food and Drug Administration

Regulations and guidance documents published by the FDA concerning women's participation in industry-sponsored clinical trials have changed

Table 1. Significant events in the history of women's participation in clinical trials in the U.S.

Year	Event
1962	Thalidomide tragedy in Europe results in United States Congress to pass the Kefauver-Harris Amendment to mandate changes in drug development and strengthen the authority of the FDA
1975	National Commission for the Protection of Human Subjects and Biomedical and Behavioral Research promulgates new rule which includes pregnant women as a vulnerable research subjects
1977	FDA guideline "General considerations for the clinical evaluation of drugs" essentially bans women of child-bearing potential from participating in early phase clinical research, except for life-threatening conditions
1985	Report from U.S. Public Health Service Task Force on Women's Health concludes "research should emphasize disease unique to women or more prevalent in women"
1986	NIH advisory committee recommends to grant applicants that women be included in studies; if women are not included, clear rationale must be provided
1988	FDA "Guideline for the format and content of the clinical and statistical sections of new drug applications" specifies the importance of examining data within NDA databases for differences in safety or efficacy in subgroup populations, including gender
1990	Office of Research on Women's Health established at the NIH
1993	FDA guideline "Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs" reverses the 1977 guidance
1993	Congress mandates adequate inclusion of women in NIH-sponsored clinical trials to determine differences between the sexes
1994	Office of Women's Health Established at the FDA
1994	IOM report, "Women and health research" calls attention to two forms of historical gender bias in the design and implementation of clinical trials
1998	FDA regulation "Presentation of safety and effectiveness data for certain subgroups of the population in investigational new drug application repots and new drug applications" states that NDAs must present safety and efficacy data by sex; FDA has the authority to refuse to file any NDA that does not analyze the safety and efficacy data appropriately by sex. Demographics of participants in its clinical trials must also be included in IND annual reports.
2000	FDA regulation "Investigational new drug applications: amendment to clinical hold regulations for products intended for life-threatening disease and conditions" gives FDA authority to place a trial for a life-threatening disease or condition on clinical hold if sponsors exclude men or women only because of reproductive potential.
2001	IOM report, "Exploring the biological contributions to women's health: does sex matter?" establishes importance of sex-based biology.
2010	IOM report, "Women's health research: progress, pitfalls, and promise" highlights areas of advancement and remaining deficiencies in women's health research

FDA= Food and Drug Administration; NIH= National Institutes of Health; IOM= Institute of Medicine

significantly over the past half century.[17] After the tragedies caused by the use of thalidomide in pregnant women, the FDA issued "General Considerations for the Clinical Evaluation of Drugs" in 1977. This guidance document stated that women of child-bearing potential should be excluded from Phase 1 and early Phase 2 research, except if these studies were being conducted to test a drug for a life-threatening illness. If a drug appeared to have a favorable risk-benefit assessment, women could then be included in later Phase 2 and Phase 3 trials if animal teratogenicity and fertility studies were finished. The term "child-bearing potential" was defined widely as any woman capable of becoming pregnant, including premenopausal single abstinent women, women using contraceptives, or women with sterile partners.[16] Advocacy groups criticized the 1977 FDA guideline by arguing that trial participation should be focused on a woman's independence to make decisions and determine fetal risks during pregnancy.[9] They noted that women were capable of helping develop medical knowledge about sex differences through participating in studies.[9] Retrospectively, the FDA, researchers, and the majority of the public now view the 1977 guidance as "rigid and paternalistic, leaving virtually no room for the exercise of judgment by responsible research subjects, physician investigators, and investigational review boards (IRBs)".[16] Concerns were voiced that this guidance may have had the unintended effect of causing a general underrepresentation of women in drug development studies.[16]

In 1993, FDA reversed the 1977 guidance with another guidance document entitled "Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." This guidance lifted the ban of women of child-bearing potential from participating in early phase research and left the decision to researchers, IRBs, and women themselves.[16] The guidance further specified that clinical trial participants should be representative of the patient population that is likely to be prescribed the drug once it is approved. The FDA articulated the importance of examining differences in safety, efficacy, pharmacokinetics, and when necessary, pharmacodynamics among population subsets.[16]

In 1998, the FDA issued a final rule entitled "Presentation of Safety and Effectiveness Data for Certain Subgroups of the Population in Investigational New Drug Application Reports and New Drug Applications". This regulation specifically states that New Drug Applications (NDA) must present safety and efficacy data for important populations, including sex, age, and racial subgroups. The FDA has the authority to refuse to file any NDA that does not analyze the safety and efficacy data appropriately by sex. The rule also calls for sponsors to report the demographics of participants in its clinical trials in Investigational New Drug Application (IND) annual reports as a means to alert either party to potential deficiencies in the NDA submission.[18] In 2000, the FDA promulgated a final rule, "Investigational New Drug Applications: Amendment to Clinical Hold Regulations for Products Intended for Life-Threatening Disease and

Conditions." This regulation gives FDA the authority to place a trial for a life-threatening disease or condition on clinical hold if sponsors exclude men or women only because of reproductive potential. This rule applies to studies involving patients with the disease or condition the drug is intended to treat; the rule does not apply to studies enrolling only health volunteers.[19]

The FDA also has an Office of Women's Health (OWH), which was created by the 1994 Congressional mandate. The OWH has two overarching goals: 1) to protect and advance the health of women through policy, science, and outreach and 2) to advocate for the participation of women in clinical trials and for sex, gender, and subpopulation analyses. The FDA OWH partners with other governmental agencies and national groups to reach out to both the scientific and lay communities.[20]

National Institutes of Health

In response to the 1985 report by the U.S. Public Health Service Task on Women's Health, the National Institutes of Health (NIH) urged the inclusion of women in clinical trials in 1987. Congress formalized this through a section of the NIH Revitalization Act of 1993 titled "Women and Minorities as Subjects in Clinical Research". Four issues were addressed: 1) that the NIH ensure that women and minorities be included in all clinical research; 2) that numbers in Phase 3 clinical trials be sufficient to allow for valid analyses of potential differences; 3) that these groups could not be excluded due to trial costs; and 4) that the NIH create programs and support outreach efforts to enroll and retain women and minorities in clinical trials. The NIH does not fund any grant or project that is out of compliance on one of these four issues.[21]

The NIH also has an Office of Research on Women's Health (ORWH), which was established in 1990. The ORWH is charged with increasing research in areas that affect women, identifying existing gaps in knowledge, and creating a national women's health research agenda for the NIH. The ORWH ensures women are adequately involved in NIH-supported research studies. Additionally, the ORWH establishes programs to increase the number of women who pursue careers in biomedical research.[22]

Progress of Women in Clinical Trials

When attempting to assess the actual number of women enrolled in clinical trials, various investigators have reached different conclusions. The numbers and percentages can vary depending on the kinds of trials included in the analyses. For example, the phase of clinical research assessed, whether trials for sex-specific conditions were included in the assessment, and the timeline when the studies were conducted all influence the perception of women's participation in such trials.[23] As a result, some published articles have stated that women are underrepresented or overrepresented in clinical trials[23], while others did not find a systematic bias against women.[24]

The FDA conducted two surveys in the 1980s to assess women as participants in clinical studies. The first, published in 1983, looked at 11 pending NDAs. The FDA determined that the proportion of men and women in later phase clinical studies was appropriate (once adjusted for age-related differences in disease expression) for the proposed indications. In 1989, FDA examined 20 NDAs and found that two did not have the right proportion of men and women in later phase clinical trials.[16]

In 1992, the U.S. Government Accountability Office (GAO) polled all drug manufacturers that obtained FDA approval for new chemical entities from January 1988 to June 1991. While women were included in the Phase 2 and 3 clinical trials for all 53 drugs, they were underrepresented (by GAO assessment) in trials for about 60% of the drugs. Trials for 36 of the 53 drugs (68%) included the minimum number of women suggested by the FDA. For 25 of the 53 drugs (47%), sponsors examined whether women and men experienced differential responses. (It is important to note that many of the drug studies were conducted and submitted to the FDA before the 1988 requirement).[25] In this assessment, no indication was found that women aged 15 to 49 years constituted a lower percentage of participants than women in other age groups, contradicting the notion that the ban on women in early phase clinical research caused a general lack of participation of women of child-bearing potential in late phase clinical trials.[16,25]

A study conducted by the Center for Drug Evaluation and Research (CDER) examined 185 new molecular entities approved by the FDA between 1995-1999. The authors concluded that women and men participated in clinical trials at levels consistent with the prevalence of the disease state studied. Examination of labeling for these products revealed that at least 68% contained some statement about sex.[26]

An analysis of 10 prescription drugs that were withdrawn in the market from 1997-2001 found that eight posed "greater health risks for women", mainly because of adverse drug events due to known pharmacodynamic differences (e.g.: three drugs withdrawn due to risk of torsades de pointes) or because of greater exposure of women to these drugs (e.g.: four drugs were prescribed to more women than men).[27] These findings resulted in another the GAO study. In 2001, the GAO published "Women Sufficiently Represented in New Drug Testing, but the FDA Oversight Needs Improvement." For this review, the GAO examined summary documents of the 36 NDAs for new molecular entities submitted to and approved by the FDA between August 1998 and December 2000. In addition, the clinical trials section of 100 randomly-selected IND annual reports were studied. The GAO found that about a third of the time, sponsors did not evaluate and/or present gender analysis in the NDA summary documents. The GAO also found that 39% of IND annual reports did not include the necessary demographic data for ongoing clinical trials. The GAO did find that women constituted the majority of drug trial participants; the percentage of

women varied with the stage of clinical research performed. Women accounted for 22% of participants in Phase 1 studies and 56% of participants in Phase 2 and 3 studies. Every NDA reviewed had enough women in the pivotal studies for a statistical determination that the drug was effective in this population.[28] The GAO also observed shortcomings in the FDA review and oversight process. The GAO felt that neither the FDA nor sponsors consistently utilized all of the sex-specific information available.[28]

Three additional studies have been more recently published in 2011 and 2013. In a study that evaluated the inclusion and analysis of sex in the results of federally-funded randomized clinical trials in nine major medical journals in 2009, researchers found most studies that were not sex-specific had an average enrollment of 37% women.[29] However, 64% of the studies did not specify their results by sex and did not explain why the influence of sex in their findings was ignored.[29] Also, a small sample of non-federally funded studies were examined and found to not be significantly different from the federally funded studies in analysis and inclusion of women.[29] Although this study did not examine all federally funded randomized clinical trials or compare the prevalence of sex in each disease state researched, the results indicated that studies were low in compliance with NIH guidelines regarding analysis and inclusion of women, and minimally improved from a similar study conducted in 2004.[29,30] Another study examined the sex-specific analysis and enrollment of women compared to the prevalence of women in each disease population in late-phase clinical trials, specifically Phase 3 trials, from 2007 to 2009.[31] The results showed that 64% of disease states had equal or greater participation based on prevalence. However, trials related to HIV, hypertension, and acute coronary syndrome had lower female enrollment in comparison with prevalence of those disease states in women. The majority of trials were found to have at least one type of sex-related analysis of safety or efficacy.[31] Even though the study only focused on late-phase clinical trials, it concluded that the FDA guidance and regulations and acknowledgment of individualized dosing procedures produced the increase of sex-specific analysis of safety and efficacy. Researchers also noted that enrollment of women in clinical trials could vary every year depending on the drugs related to each disease being studied.[31] The results of these two studies, both with limitations, may indicate that the inclusion of women in clinical trials has increased; however, trials are still lacking in recruiting participants similar to the prevalence in disease state and in performing sex-specific analyses. Most recently, the FDA also issued a report, "Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products". For all 30 CDER applications reviewed from 2011, demographic information by sex for key clinical trials were available in public documents, and almost all included subset analysis data by sex. Information on clinically significant demographic subset data was included in approved product labeling. The FDA concluded that, in general, populations were included in clinical trials by age and sex in similar numbers to the population distribution for the disease indications studied.[32]

Specific disease states that impact women have had substantial progress in prevention, diagnosis and treatment over the years.[3] This includes breast cancer, cervical cancer, and cardiovascular disease. Other disease states such as depression, lung cancer, and Alzheimer's disease have made less progress.[3] Looking specifically at cardiovascular disease, most early research was conducted on men even though the leading cause of mortality in women has been cardiovascular disease since 1989.[3] Trials focusing on the prevention of cardiovascular disease conducted only in women have had impact clinically. These include the Women's Health Initiative and Women's Health Study. [33] Other trials designed for both men and women include using vitamin D and omega-3 supplements or HMG-CoA reductase inhibitors ("statins") for cardiovascular disease prevention. Specific examples of advancements in the treatment of women include the comparable use of beta-blockers and aspirin after myocardial infarction (MI) in women to men, which was not observed previously, and the advantage of adding on pharmacotherapy during percutaneous coronary intervention.[3] Yet the amount of women enrolled in clinical trials related to cardiovascular disease in proportion to its prevalence is still lacking even though participation has increased.[33] Additionally, although studies on the intervention for MI and acute ischemic syndromes have been used clinically in women, the reliability of their conclusions because of insufficient statistical power is uncertain.[33] Subsequently, although the inclusion of women in cardiovascular research has increased, understanding of sex differences is still wanting.[3]

CURRENT EFFORTS

There are numerous initiatives in the U.S. that continue to address the issue of women in clinical trials. While not intended to be comprehensive, the examples listed below highlight some of the ways the FDA and NIH remain focused on this issue.

The FDA has several ongoing projects that could improve the ability to identify sex differences. One is the Critical Path Initiative, the goal of which is to modernize drug development through use of innovative tools and techniques.[13] Through the use of biomarkers to estimate potential safety or efficacy outcomes, advanced technologies, applications of pharmacogenomics, and new trial designs and data analysis techniques, there may be greater opportunity to identify subpopulation differences in response. Additionally, more robust use of information technology will enable better characterization of data and better identification of potential clinical trial participants.[13] The FDA also has an "Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data". Twenty-seven action items comprise the plan, which has three main priorities: 1) quality - to improve collection, reporting, and analysis of demographic subgroup data; 2) participation - to identify barriers

Table 2. National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) strategic plan goals[38]
Goal 1: Increase sex differences research in basic science studies
Goal 2: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs
Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women
Goal 4: Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research
Goal 5: Develop and implement new communication and social networking technologies to increase understanding and appreciation of women's health and wellness research
Goal 6: Employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce

to enrollment for members of subgroups and to implement programs to encourage enrollment; and 3) transparency – to make data by demographic subgroup more available.[34] One program recently launched to improve transparency is Drug Trial Snapshots, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm. This consumer-friendly website provides information on subpopulation involvement in the pivotal clinical trials for newly-approved drugs and whether any differences in benefits or risks of drug use by subpopulation were observed.[35] The FDA continues to educate and train their staff regarding reporting, analyzing, and communicating data by subpopulation, and to partner with industry and other groups such as the NIH to identify best practices and overcome barriers.[36]

To facilitate enrollment of women in clinical trials, the NIH has created an Outreach Notebook with five outreach elements related to population considerations, outreach preparation, research agreements, developing evaluations and sustaining communication.[37] In addition, the Advisory Committee on Research on Women's Health's (ACRWH) recent biennial report observed progress in the ORWH's Strategic Plan of six goals (Table 2) each with their objectives.[38] Focusing on Goal 1, which is most related to women in clinical trials, the ORWH partnered with Institutes and Centers of the NIH to encourage important research enterprises in women's health by co-funding projects in various medical fields with the NIH and using specific ORWH programs to review research applications and research.[38] The ORWH introduced two programs: the Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health and Building Interdisciplinary Research Careers in Women's Health (BIRWCH). Both serve to develop interdisciplinary research and careers in women's health research.[38]

CONSIDERATIONS FOR THE FUTURE

There are many potential areas for research in women's health. Continued investigations in the areas of sex-based biology, differences in healthcare needs between men and women, recognition and reduction of health disparities between men and women, and evidence-based information to assist women while making healthcare decisions are all areas of need.[1,39] There are considerations for the enrollment and retention of women in clinical trials, the design of trials, and the expectations of journals that may help to close some of the existing gaps seen today.

While there are thousands of clinical trials enrolling annually, women are less likely to be aware of or to participate in clinical trials.[40] There are various reasons contributing to the lack of participation of not only women, but also of minorities, in clinical trials.[37] From past history of unethical research, apprehension and cynicism towards clinical trials may exist in communities. The transportation capability to travel to and from research facilities may complicate the ability to participate in clinical studies, especially for those living in rural areas. Subjects may find that taking time to partake in these trials may interfere with both family and work obligations. There also may be "subject burden" where the constant travel and medical testing may be exhausting for enrollees.[37] Financial burdens such as poverty or a low-income status may limit subjects, especially minorities, from participating. Furthermore, there are extra challenges with the addition of diversity in clinical trials relative to communication and cultural attitudes.[41]

Researchers need to address these challenges and utilize available tools to facilitate enrollment of women in clinical trials (Table 3). Logistically, clinics may need to be open at flexible hours or follow-up may need to be performed at the participant's home, rather than at the clinic.[4] Childcare or transportation should be offered or reimbursed, per IRB approval. Reaching out to women through IRB-approved advertising in places such as salons, gyms, stores, laundromats, and churches may be helpful. Diverse staff should be recruited, if possible; all staff should be made aware of the distinct needs of women in clinical trials. Additional time should be allotted to review informed consent with women, considerations for which are described below. Their contributions should be acknowledged, and feedback should be gathered from women at the conclusion of the trial to inform future efforts.[4]

Researchers must also have special considerations when enrolling fertile women. The FDA expects that women of child-bearing potential enrolled in a clinical trial will take the necessary precautions to avoid pregnancy during drug exposure, the length of which may surpass the actual length of the study.[16] Therefore, women participating in the trials must have access to counseling and medical care for contraception.[14,16,42] Investigators must verify that a woman participating in the trial is not pregnant and monitor for pregnancy.[14,16,42] As much detail as possible must be given in the informed consent document about the potential risks to a fetus from the investigational drug.[16] If no pertinent data available, the document should clearly state the potential for fetal risk. Researchers may also be

Table 3. Selected resources for clinicians, academicians, and researchers
Sex-based Biology • Web-based Training Courses: The science of sex and gender in human health (joint project with the NIH Office of Research on Women's Health) Available at https://sexandgendercourse.od.nih.gov/ • IOM. "Exploring the biological contributions to women's health: does sex matter?" 2001. Available at http://www.nap.edu/catalog/10028/exploring-the-biological-contributions-to-human-health-does-sex-matter • IOM. "Women's health research: progress, pitfalls, and promise". 2010. Available at http://iom.nationalacademies.org/Reports/2010/Womens-Health-Research-Progress-Pitfalls-and-Promise.aspx
Curricula Guides • "Beyond women's health: incorporating sex and gender differences into graduate public health curricula". Available at: http://www.aspph.org/wp-content/uploads/2014/06/Womens-Health-FINAL.pdf • Women's health curricula: final report on expert panel recommendations for interprofessional collaboration across the health professions. Available at: http://www.aacn.nche.edu/education-resources/HRSA-Womens-Health-Curricula-Report.pdf • Women's health curriculum and toolbox jointly developed by American Association of Colleges of Pharmacy and FDA OWH. Available at http://www.aacp.org/RESOURCES/EDUCATION/WHC/Pages/default.aspx
Women's Health Resources • Women's health resources web portal. Available at: http://orwh.od.nih.gov • FDA OWH. Available at: http://www.fda.gov/ForConsumers/ByAudience/ForWomen/default.htm • U.S. Department of Health and Human Services OWH. Available at http://www.womenshealth.gov/index.php
Clinical Trial Materials • NIH Outreach notebook for the inclusion, recruitment and retention of women and minority subjects in clinical research. Available at http://orwh.od.nih.gov/research/inclusion/pdf/Outreach-Notebook-021315.pdf • NIH outreach toolkit: how to engage, recruit, and retain women in clinical research. Available at http://orwh.od.nih.gov/toolkit/ • FDA Women in Clinical Trials. Available at http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118508.htm • The Society for Women's Health Research and FDA OWH. Dialogues on diversifying clinical trials successful strategies for engaging women and minorities in clinical trials. Available at: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM334959.pdf • National Institute on Drug Abuse Treatment Clinical Trials Network: Successfully including women in clinical trials, a guide for researchers. Available at https://www.drugabuse.gov/sites/default/files/womens-brochure_1025-004_508.pdf
FDA= Food and Drug Administration; IOM: Institute of Medicine; NIH= National Institutes of Health; OWH= Office of Women's Health

able to reduce the risk of fetal exposure through study design.[4]

Multiple considerations may complicate the researcher's task of designing trials to conduct sex analysis of their findings.[43] This includes the difficulty of estimating and recruiting a large enough sample size to have a sufficient power for subgroup analyses. This indicates that the percentage of female subjects is not the only concern. Without appropriate power, the application of study results is limited. Researchers also need to look forward to considering reproductive endocrinology as a variable in test subjects.[43] The female population in a study may be further allocated by their hormonal status, menopausal status. And contraceptive use, but researchers may not be cognizant about these endocrine factors. Different statistical methods such as the Bayesian statistical inference test have been suggested as better tailored towards sex-analysis rather than frequentist statistics and null-hypothesis errors. Consequently the question remains of the best way to statistically analyze differences between sexes. Using new methodologies would result in the necessity of researchers and clinicians to be educated on the statistical methods to understand findings. In terms of statistical significance, having enough women to establish statistical power has not been successful since the estimation and likelihood of achieving the sample size needed is difficult.[43] The inexperience of conducting sex-based research among researchers is an issue as well.[33]

Also, new methods of design and analysis associated with requirements from medical journals or governmental agencies warrant further discussion to help ensure consistent sex-specific analysis of data.[43] For example, journal editors and editorial associations especially have an ability to establish policies for authors to consider sex-analysis when designing and reporting clinical trials.[43] Revised publishing standards for journals may also encourage more researchers to analyze data by sex. Most standard guidelines and editorial associations for researchers do not require reporting sex-specific results. The Journal of the National Cancer Institute became the first journal to ask authors to, when appropriate, conduct subgroup analyses by sex and ethnicity in clinical and epidemiological studies. If there is no difference, it should be stated in the Results section. Any editorial policy changes should be carefully considered to minimize unintended consequences.[43]

Lastly, further advancement of women in clinical research may require not only the continued leadership of government agencies, but also input from other stakeholders such as policymakers, healthcare professionals, educators, advocacy organizations, and funding organizations.[33] By promoting health equity through developing research requirements for design and analyses of clinical trials and improving understanding how clinical outcomes are affected by sex, further progress in women's health can be made.

SUMMARY

Many groups, including the FDA, NIH, clinicians, academia, Congress, industry, and advocacy groups, have an interest in ensuring appropriate enrollment of women in clinical trials and sex-specific analysis of the data. It is critical that data from women are available when decisions on dosing, safety, and efficacy of therapeutic agents are being made. In the U.S., there has been a shift in philosophy in how to best protect public's health. Instead of simply excluding women of child-bearing

potential from participation in early phase research, it is now recognized that risk can be mitigated by responsible research practices. Although history has displayed a lack of representation of women in clinical trials, U.S. governmental agencies have sought to establish guidelines, policies, and organizations to encourage researchers to increase the quality of women's health research. Through these efforts, the medical field will be able to identify sex differences, which includes the response of medications relative to safety and efficacy, to carefully direct clinical decisions. While there are still barriers and questions that continue to be addressed, women's health research continues to advance.

CONFLICT OF INTEREST

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