American Heart Association | American Stroke Association

March 19, 2012

Division of Dockets Management
HFA-305
Food & Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: FDA-2011-D-0817 (Draft Guidance for Industry and FDA Staff; Evaluation of Sex Differences in Medical Device Clinical Studies)

Dear Director Shuren and CDRH Staff:

On behalf of the American Heart Association (AHA), including its American Stroke Association (ASA) division and more than 22.5 million AHA and ASA volunteers and supporters, we appreciate the opportunity to provide comments on the proposed draft guidance on the study and evaluation of sex differences in medical device clinical studies.

AHA applauds the Food and Drug Administration (FDA) for issuing this draft guidance, which we believe is a significant step in the right direction and long overdue. Although important progress has been made since the Institute of Medicine (IOM) issued its landmark 2001 report, *Exploring the Biological Contributions to Human Health: Does Sex Matter?*, there are still significant gaps in the participation of women in clinical trials, the analysis of sex differences, and the availability of sex-specific data to clinicians, researchers, and patients, particularly with respect to early phase trials and device trials. These gaps caused an IOM Committee to conclude in its 2010 report, *Women's Health Research: Progress, Pitfalls, and Promise*:

> "There also has been inadequate enforcement of requirements that representative numbers of women be included in clinical trials and that results in women be reported. Lack of taking account of sex and gender differences in the design and analysis of studies, and a lack of reporting on sex and gender differences has hindered identification of potentially important sex-differences and slowed progress in women's health research and its translation to clinical practice."[1]

We strongly urge the FDA to act as quickly as possible to finalize and strengthen this guidance. We also have a number of both overall and specific recommendations for improving it.

Although we appreciate that FDA is proposing this action and we recognize that guidance allows FDA to make specific recommendations that may not be feasible in the form of regulation, we are concerned that guidance does not have the same force as law or regulation and will be less effective. Therefore, we strongly urge FDA to consider issuing complementary proposed regulations that would require sex-specific statistical analysis and establish legally enforceable responsibilities in this area. FDA regulations already exist that require new drug applications (NDAs) and investigational new drug (IND) annual reports to present safety and effectiveness data by gender, as well as age and race, but corresponding regulations do not exist for medical devices, and we believe they should.

In addition, history unfortunately suggests that guidance may not be sufficient for achieving the goals hoped for with this latest proposed guidance. In 1994, the FDA instituted a directive that all submissions seeking new device approval must contain a gender-bias statement and information about the differences in the safety and effectiveness of the device in women. A recent editorial in the *Journal of the American Medical Association (JAMA)* pointed out that it still has not been fully implemented nearly 20 years later:

> "However, an examination of compliance with this directive found that it is routinely ignored. Among 78 high-risk cardiovascular devices approved during the years 2000 through 2007, the overall patient population in these studies was 67% men with no increase in the enrollment of women over time, although women make up 46% of all patients with cardiovascular disease. The analyses by sex specified in the 1994 FDA directive occurred in only 41% of studies (51/123)."[2]

Why Action Is Needed

Cardiovascular diseases (CVD) are the leading cause of death of American women, as well as men. Although we've made significant progress overall in the reduction of CVD mortality, that progress has been uneven. In particular, women have seen their death rate from CVD decline more slowly than it has among men.[3]

Researchers have learned that sex differences play an important role in the prevention, diagnosis, and treatment of heart disease, stroke, and other forms of CVD. For instance, heart attack symptoms may be different in women than in men. Women also tend to develop CVD later in life. There are also disparities in outcomes between women and men. For example, women age 45 and older are less likely than men of that age group to survive a year after their first heart attack (74 percent vs. 81 percent).[3]

A lack of adequate information about the safety and effectiveness of options for the prevention, diagnosis, and treatment of CVD in women contributes to the health disparities they face. Women continue to be underrepresented in clinical research studies, making it difficult to evaluate whether study findings apply to them. While some progress has been made in improving women's participation

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

[2] Dhruva SS and Redberg R. Evaluating Sex Differences in Medical Device Clinical Trials: Time for Action. *JAMA.* Published Online: February 29, 2012. doi:10.1001/jama.2012.254.

[3] Roger VL, Go AS, Lloyd-Jones DM, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125.

in drug clinical trials, women continue to be persistently underrepresented in cardiovascular device trials. As referenced above, an analysis of more than 120 studies of 78 medical devices approved by FDA between 2000 and 2007 found that women made up only one-third of the studies' participants, on average, and 28 percent of the studies didn't provide the gender of the patients enrolled in the trials.[4]

Women also continue to be underrepresented in early phase clinical trials. For example, a 2010 study found that the percentage of women participating in early phase trials has increased only to 31 percent.[5]

Even when there is adequate representation of women and minorities in clinical studies, sex or race-specific information is often not publicly reported, making it difficult for researchers, clinicians, and their patients to draw conclusions. One study found that three-fourths of CVD clinical trials do not report sex-specific results.[6]

Recommendations for Achieving Representative Enrollment

We support the FDA's recommendation that clinical studies strive to enroll representative proportions of women and men, consistent with the disease's prevalence in the underlying population. While we certainly understand the need to conduct clinical trials in a timely and cost-effective manner, adequate representation of patient subgroups that will ultimately be using the device is critical to ensuring that it is safe and effective for all people.

We particularly applaud the recommendations for new or ongoing device studies to proactively and prospectively develop a plan to enroll sufficient proportions of women and men in clinical research. As the FDA guidance recognizes, there are many reasons why women (as well as minorities and older adults) may not participate in clinical research at levels equal to men, and we recognize that trial sponsors should have flexibility in adopting strategies to enhance their participation in ways most appropriate for their study. However, we specifically support the approach of encouraging trial sponsors to set and reach certain minimum enrollment levels for women, such as by maintaining open enrollment for women until a pre-specified proportion is reached.

Another strategy not specifically mentioned in the FDA's guidance is to increase the number of female physicians participating in clinical research. Female physicians treat a higher proportion of female patients than do their male counterparts, but only about 10 percent of female physicians participate as principal investigators in clinical research.[7]

We also recommend the close monitoring of study participants and the use of proactive strategies to retain participants as a cost-effective means of achieving participation goals. Previous studies have experienced higher drop-out rates among women and African-Americans, compared to their male and white counterparts. The 2010 IOM report on women's health research suggested that one possible mechanism for monitoring participation, efficacy, and adverse outcomes would be expansion of the role of data safety monitoring boards.[1]

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[4] Dhruva SS, Bero L, and Redberg R. Gender Bias in Studies for Food and Drug Administration Premarket Approval of Cardiovascular Devices. *Circ Cardiovasc Qual Outcomes.* Published online ahead of print March 1, 2011.

[5] FDA. Status of Women's Participation in Clinical Trials. *Journal of Women's Health,* 2010; 19:1771.

[6] Blauwet LA, et al. Low rate of sex-specific result reporting in cardiovascular trials. *Mayo Clin Proc*. 2007;82:166-170.

[7] Tufts Center for the Study of Drug Development. *Notable gender and racial disparities exist among clinical investigators.* Volume 9, Number 6. November/December 2007.

To reinforce the importance of the participation of sufficient numbers of women and the performance of sex-specific analysis, FDA should exercise its existing regulatory authority to return new device applications that do not submit the required information.

We also recommend that FDA consider including guidance on the participation in clinical studies of transgender and other individuals for whom gender identity may not be captured by "male" or "female" categories. It is necessary for these individuals to be addressed in the FDA's guidance so that they will not be excluded from clinical research.

Recommendations for Sex-Specific Statistical Analysis

We strongly support the FDA's recommendations for investigating and reporting differences in study outcomes of treatment by sex. Such an analysis will provide helpful information for treating both women and men.

We particularly appreciate the FDA's recognition that, if results of study analysis suggest there is insufficient data to assess whether sex is associated with differences in outcome, additional clinical data may be needed pre- or post-market to address potential sex-specific questions related to safety or effectiveness. To determine whether this is necessary, FDA should actively monitor compliance with sex-specific subgroup analyses by primary effectiveness endpoint(s); primary safety endpoint(s); and key secondary endpoints.

Recommendations for Reporting Sex-Specific Information in Summaries and Labeling

Researchers, clinicians, and their patients need publicly available information about the safety and effectiveness of specific therapies by demographic subgroup. We therefore strongly support your recommendation that the results of sex-specific analyses should be presented in the labeling, even if these analyses suggest no sex differences in outcomes. If the proportion of women participating in the trial is not sufficient to evaluate whether sex differences exist, we recommend that this be stated on the label as well.

Additional Comments

Going forward, we would also like to work with the FDA on comparable guidance or regulations in the future that would help address similar concerns about the under-representation of racial and ethnic minorities and elderly individuals in clinical research. Although FDA notes in several places throughout the draft guidance that some of its recommendations may also be used to promote study enrollment and adequate analysis of study data for other demographic variables, such as age, race and ethnicity, a stronger emphasis on the inclusion of older and minority participants is warranted. A recent review of racial and ethnic differences in cardiac care found that 91 percent of high quality studies included data on blacks, but only 26 percent of studies included data on Hispanics, 14 percent on Asians, and a mere 5 percent on Native Americans.[8] Similarly, even though 43 percent of acute coronary syndrome (ACS) patients are age 75 or older, half of ACS trials conducted between 1996 and 2000 did not include a single patient over age 75.[9]

[8] The Kaiser Family Foundation and the American College of Cardiology Foundation. Racial/Ethnic Differences in Cardiac Care: The Weight of the Evidence. (Report #6040, available at www.kff.org).

[9] Dodd KS, et al. Exclusion of older adults and women from recent trials of acute coronary syndromes. *J Am Geriatr Soc*. 2011 Mar; 59(3):506-11)

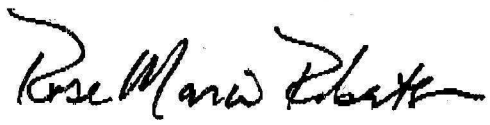
Conclusion

In closing, AHA reiterates our appreciation of the FDA's guidance to further the evaluation of sex differences in medical device clinical studies. To optimize the goals of this guidance, we recommend that it be finalized as quickly as possible and that FDA consider issuing complementary regulations to require sex-specific statistical analysis. FDA should also put in place procedures to track compliance with these recommendations and take further action as needed to ensure compliance. Moreover, the results of subgroup-specific analyses should be included in the labeling so that it is accessible to researchers, clinicians, and patients. Finally, we also recommend that FDA also develop guidance that speaks to the need for greater participation of racial and ethnic minorities and older adults in clinical research.

We are eager to work with the FDA to strengthen its guidance and enforcement in this area and to offer any assistance you may require. If you have any questions or need any additional information, please do not hesitate to contact Stephanie Mohl, government relations manager, at (202) 785-7909 or stephanie.mohl@heart.org.

Thank you for your consideration of our comments.

Sincerely,



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