Draft Guidance for Industry and Food and Drug Administration Staff

Evaluation of Sex Differences in Medical Device Clinical Studies

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

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Evaluation of Sex Differences in Medical Device Clinical Studies

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

This document provides guidance on the study and evaluation of sex differences in medical device clinical studies.

The purpose of this guidance is to outline the Center for Devices and Radiological Health's (CDRH) expectations regarding sex-specific patient enrollment, data analysis, and reporting of study information. The intent is to improve the quality and consistency of available data regarding the performance of medical devices in both sexes by ensuring appropriate representation by sex in clinical studies of devices, and that data from such studies is appropriately analyzed for sex differences. This information can be of benefit to patients and their medical providers, as well as clinical researchers and others. The specific objectives of this guidance are: 1) to provide recommendations for study design and conduct to encourage enrollment of women in proportions that are representative of the demographics of disease distribution; 2) to outline recommended statistical analyses of study data for sex differences, and to identify sex-specific questions for further study; 3) to encourage the consideration of sex and associated covariates (e.g., body size, plaque morphology, etc.) during the study design stage; and 4) to specify CDRH's expectations for reporting sex-specific information in summaries and labeling for approved devices.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and

should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Scope

This guidance is intended for devices that require clinical information in support of a marketing submission, whether a premarket notification (510(k)), premarket approval (PMA) application or humanitarian device exemption (HDE) application. The recommendations contained herein also apply to post-approval study (PAS) submissions and postmarket surveillance (PS) studies conducted in accordance with Section 522 of the Food, Drug and Cosmetic Act., where noted.

Sex is not the only demographic variables which may have an impact on device performance. This guidance focuses on the impact of sex; however, some of the recommendations in this guidance may also be used to promote study enrollment and data analysis that adequately accounts for other demographic variables, such as age, race, and ethnicity.

The impact of demographic variables may apply more to certain types of products or diseases than others. For example, certain OB/GYN and urology devices may be intended for use in single-sex populations so studies of these devices would not be expected to address the potential for sex differences in outcome.

FDA recommends the use of this guidance document as a supplement to other CDRH guidance, in particular, any relevant device-specific guidance. Consultation with the CDRH primary reviewing division is advised.

III. Foreword

Certain elements described in this guidance have been emphasized in Agency regulations and/or policy in the past. Over recent decades the views of the Agency, as well as those of the medical community in general, have evolved regarding women in clinical studies.

Recently, CDRH publicly sought input from a variety of experts and stakeholders regarding the study and evaluation of women in clinical studies for medical devices. On June 2, 2008, various government agencies, physician professional societies, and patient advocacy groups participated in a public workshop to discuss ways to overcome barriers to understanding the impact of sex differences on clinical outcomes, with a focus on clinical study conduct and statistical analysis.[1] On December 9, 2008, CDRH and an industry trade association co-hosted a second public meeting, to facilitate discussion in anticipation of issuance of FDA guidance on this subject.[2] This guidance document reflects the recommendations generated in these public workshops and subsequent internal Agency discussions. It is intended to

[1] http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm111139.htm
[2] http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm111137.htm

provide guidance for the design and conduct of clinical studies to improve information about the safety and effectiveness of new medical devices in women when approved by the FDA.

The terms *sex* and *gender* are often used interchangeably in the scientific literature and popular press. However, according to a 2001 consensus report from the Institute of Medicine, the terms have distinct definitions which should be used consistently to describe research results.[3] The differences of greatest interest to CDRH are those associated with biological factors (*sex*[4]); however most medical device studies use patient self-reported values for this variable (*gender*[5]). For the purposes of this guidance document we use the term *sex*, with the understanding that for most medical device studies *gender* is used as a surrogate for *sex*. This guidance focuses on addressing potential differences in study design, conduct, outcomes, and interpretation that should be considered to ensure sex-specific issues are adequately addressed in clinical studies.

A. Why consider sex differences?

Certain medical products elicit different responses in women compared to men. Differences may be attributable to intrinsic factors (e.g., genetics, hormones, body size, sex-specific physiology), extrinsic factors (e.g., diet, sociocultural issues, environment) or interactions between these factors. For example, there may be medical conditions that are unique to a certain sex, ethnic or racial group which should be considered in study recruitment and in reporting of results.

Covariates associated with female sex (e.g., size, age, comorbidities, past pregnancies) may be responsible for certain differences in safety, effectiveness, or design attributes such as failure mode. Furthermore, fluctuations associated with hormonal changes (e.g., onset of puberty, menstrual cycle, menopause, oral contraceptive or hormone replacement therapy use) may interact with clinical outcomes. Additionally, the menstrual cycle is associated with hormonally-mediated differences in metabolism or changes in fluid balance which could lead to intra-subject variability.

Examples where sex differences impact FDA's regulatory considerations:

1. Ventricular Assist Devices (VADs) provide mechanical circulatory support for patients with heart failure. One study of a next-generation VAD showed that in subjects treated with the investigational device, female sex or covariates associated with sex (body surface area, BSA) were found to be correlated with a higher rate of stroke in females as compared to males (18% vs. 6%). There were also trends toward increased rates of bleeding and infection in females

[3] Institute of Medicine, Committee on Understanding the Biology of Sex and Gender Differences. *Exploring the Biological Contributions to Human Health: Does Sex Matter?* National Academy of Sciences, 2001.
[4] *Sex* refers to the classification of living things, generally as male or female according to their reproductive organs and functions assigned by chromosomal complement.
[5] *Gender* refers to a person's self representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation. Gender is rooted in biology, and shaped by environment and experience.

compared to males. There did not appear to be differences in primary effectiveness outcome of survival (to cardiac transplantation or 180 days of support while being listed as status UNOS 1A/1B for transplant). The strength of these conclusions is somewhat limited by the sample size (150 men and 44 women). The FDA Advisory Committee recommended that a post-approval study be conducted which would include adequate collection of data regarding both sex and body surface area to determine if differences exist in device performance. (Thoratec HeartMate II, Summary of Safety and Effectiveness: http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040b.pdf)

2. Cardiac Resynchronization Therapy Defibrillators (CRT-D) provide two functions. As an implantable cardioverter defibrillator (ICD) it senses dangerous abnormal heart rhythms and then attempts to shock the heart back into a normal rhythm. As cardiac resynchronization therapy, it generates small electrical impulses to coordinate the beating of the left and right ventricles so that they work together more effectively to pump blood throughout the body. One study demonstrated that the benefit of CRT-D therapy over ICD alone (benefit defined as reduction in the composite endpoint of all-cause mortality or first heart failure event) was greater in women than men (77% versus 42%). Left Bundle Branch Block (LBBB) is a marker of an electrical conduction disorder in the heart and has been associated with a greater benefit in patients receiving CRT; the proportion of subjects with LBBB in this study was significantly greater in women than men (87% versus 65%). These findings are considered exploratory since the sex-specific analysis was *post hoc*. There did not appear to be differences in primary safety outcome of system-related complication-free survival within 91 days post implant. The FDA Advisory Committee recommended that two post-approval studies be conducted that would include adequate collection of data regarding the effects of the therapy in patients fulfilling the approved indication.

B. Participation of Women in Clinical Studies

Historically, women have been under-represented in or excluded from many clinical studies. This has led to a lack of information available for women and their physicians regarding the risks and benefits of many medical treatments and diagnostic procedures.

1. Lack of Available Data for Women

In the mid-1970s, legislation and subsequent regulations and guidelines conveyed recommendations by the FDA and many in the medical and scientific community that women "of child-bearing potential" be excluded from drug studies to protect the fetus from exposure to unknown drugs.[6] However, it soon became apparent

[6] U.S. Department of Health, Education, and Welfare, "General Considerations for the Clinical Evaluation of Drugs, HEW (FDA) 77-3040" (Government Printing Office, Washington, September 1977).

that this policy contributed to "compromis[ing] the quality of health information available to women as well as the health care they receive."[7]

The Government Accounting Office (GAO) audited clinical study information submitted to FDA in support of drug marketing applications, and concluded in a 1992 report that women were significantly underrepresented, and sex-specific data analysis was performed in less than 50% of drug studies.[8] That same year, the FDA issued a "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" which encouraged participation of women in early phase (dosing) studies, required data collection on sex differences, and encouraged consideration of the effect of menstrual cycle and potential interaction with oral contraception or hormone replacement therapy. In 1994, the Center for Devices and Radiological Health (CDRH) discussed addressing the possibility of "gender bias" in submissions and review documentation for new medical devices.[9]

A 2001 report by the GAO on FDA-reviewed drug studies found that women accounted for 52% of total study enrollees, but approximately 30% of the study documents examined did not report outcomes by sex, and almost 40% did not report enrollment demographics.[10] Since then, the FDA Office of Special Health Issues published a 2003 report which showed improvements in the inclusion of women and sex-specific analysis and reporting in drug studies for most medical areas except AIDS, oncology, and heart disease.[11]

In medical device studies, an evaluation of cardiovascular PMAs reported in 2009 showed persistent underrepresentation of women. Pivotal studies that reported sex enrolled an average of 33.9% women.[12]

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[7] Women's health. Report of the Public Health Service Task Force on Women's Health Issues. Public Health Rep. 1985 Jan–Feb; 100(1): 73–106.

[8] United States General Accounting Office. Women's Health. FDA Needs to Ensure More Study of Gender Differences in Prescription Drug Testing. (Accessed April 2, 2010 at http://archive.gao.gov/d35t11/147861.pdf).

[9] CDRH ODE Annual Report FY1994.

[10] United States General Accounting Office. Women's Health. Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement. (Accessed April 2, 2010 at http://www.gao.gov/new.items/d01754.pdf, ed,: 2001).

[11] Evelyn B, Toigo T, Banks D, Pohl D, Gray K, Robins B, Ernat J. Women's Participation in Clinical Trials and Gender-Related Labeling: A Review of New Molecular Entities Approved 1995-1999. June 2001. (Accessed September 28, 2010 at http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ParticipatinginClinicalTrials/ucm197788.htm.)

[12] Kramer DB, Mallis E, Zuckerman BD, Zimmerman BA, Maisel WH. Premarket Clinical Evaluation of Novel Cardiovascular Devices: Quality Analysis of Premarket Clinical Studies Submitted to the Food and Drug Administration 2000–2007. *Am J Therapeutics.* 2009.

2. Barriers to Enrollment of Women

Women may be less likely to enroll in clinical studies. There are myriad suspected reasons for the continued under-representation of women in clinical studies in certain product areas. The following list summarizes some of the key reasons suggested at the June 2008 FDA workshop:

- Fear of fetal consequences if the woman becomes pregnant (e.g., effects of radiographic assessments or concomitant drug therapy).
- Lack of understanding about differences in disease etiology and pathophysiology may lead to under-diagnosis and under-referral of women.
- Avoidance of female patients by investigators and sponsors due to the perception that it takes more time and money to recruit them.
- Inclusion/exclusion criteria that may not be necessary to define the study population may unintentionally exclude women (e.g., upper age limit).
- Family responsibilities which limit ability for time commitment to study follow-up.

In addition to the list above, in a 2009 report to Congress, FDA further identified barriers to the participation of subsets of the general population and medically underserved populations. This report included public comments submitted in response to a Notice in the Federal Register (74 FR 1695) seeking information on specific impediments to participation of certain groups in clinical studies; what practices currently exist to increase participation in clinical studies; and whether additional approaches are necessary to increase the participation of certain subsets of the general population in clinical studies. The recommendations and best practices submitted in response to the FR Notice, along with FDA's identification of particular areas of concern, are summarized in Part II of the report to Congress.[13]

Sponsors are encouraged to periodically examine screening logs for all patients who are screened but not ultimately enrolled in studies and to track reasons for non-enrollment of women or other key demographic groups. It may be informative to evaluate whether the demographic distribution varies at different key time points (e.g., at screening, after evaluation of study inclusion/exclusion criteria, after consent, and at various follow-up time points). For example, if the proportion of women drops

[13] See Report to Congress; Food and Drug Administration Amendments Act (FDAAA) of 2007, Public Law No. 110-85 Section 901 of the Federal Food, Drug, and Cosmetic Act; Direct-to-Consumer Advertising's Ability to Communicate to Subsets of the General Population; Barriers to the Participation of Population Subsets in Clinical Drug Trials. Available online at: http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/FDAAAImplementationChart/UCM213016.pdf.

significantly after informed consent is obtained, this may suggest that a tailored informed consent approach could improve the representation of women in the study. This information can provide insight into methods to substantially lower barriers to enrollment of women (e.g., tailored informed consent documents, flexibility in follow-up visit scheduling with consideration of child care or elder care services during appointments). Changes to a study protocol and informed consent may be made based on this information with appropriate notification to and approval from the IRB and FDA, where necessary.

Sponsors may also wish to consider resources developed by the National Institutes of Health,[14, 15, 16] or discussion with academic and contract research organizations, and high-enrolling clinical study sites, to determine practices best suited to achieve demographically representative enrollment, and to provide investigator training about these techniques.

Some specific examples of strategies to increase inclusion are discussed in Section IV.B below.

IV. Recommendations for Achieving Representative Enrollment

Many clinical studies do not enroll proportions of women that reflect the underlying disease distribution in the affected population. This can be problematic because the ability to detect differences in response to treatment is markedly diminished if there is no or limited clinical experience with the product in the subgroup of interest. This has contributed to a substantial lack of available data regarding the risks and benefits of medical device use in women. FDA recommends that you strive to enroll representative proportions of women and men (i.e., consistent with disease prevalence) to improve the quality and consistency of available sex-specific data for your device.

A. Consideration of Potential Sex Differences

To understand any potential sex differences which may be relevant to the clinical evaluation of your device, we recommend that you provide background information on

[14] NIH Office of Research on Women's Health has a number of publications available which provide advice on inclusion criteria, an overview of key elements in recruitment and retention, and a number of practical applications for conducting human subjects research, including ethical considerations. Available online at: http://orwh.od.nih.gov/inclusion/incloutreach.html.

[15] The National Institute of Mental Health developed a resource document which outlines common issues that can impact clinical recruitment and retention, and strategies to address these issues. Available online at: http://www.nimh.nih.gov/research-funding/grants/recruitment-points-to-consider-6-1-05.pdf.

[16] The National Cancer Institute developed an online resource designed for practicing professionals to support clinical trial accrual needs. The Web site is a repository for literature and other resources and serves as a 'community of practice' to encourage dialog and discussion. Available online at: http://accrualnet.acscreativeclients.com/.

the following for the disease or condition which your device is intended to treat or diagnose:[17]

- sex-specific prevalence;
- sex-specific diagnosis and treatment patterns;
- identification of proportions of women included in past studies for the target indication;
- identification of any known clinically significant sex differences in outcomes related to either safety or effectiveness

This information should be included in your study and submission documents as described in the following sections.

1. For New or Ongoing Studies (IDE study design/early enrollment stage)

You should include the information described above as part of the risk analysis section of your investigational plan (see 21 CFR 812.25(c)). We also recommend that you summarize this information in your study protocol and investigator training materials to explain the importance of enrolling representative percentages of women. For studies which are already enrolling under an approved (or conditionally approved) IDE, we recommend that this information be communicated to investigators via revised training materials or other regular communication (mailings, investigator teleconferences, etc.).

2. For Completed Studies (marketing application stage)

You should include this information as part of your marketing application in sections containing results of clinical investigations. A summary of this information should also be included in your draft PMA Summary of Safety and Effectiveness or 510(k) Summary, and in your labeling (see Section VI below for more details).

3. For Postmarket Studies (PAS or 522 PS stage)

You should include this information in interim reports and in the results section of your final report. If warranted, you should also submit revised labeling to include this information.

B. Study Design and Conduct

Women are often under-represented in clinical studies; therefore, the approaches described below are aimed at increasing enrollment of women in your study. However, in fields where men may be under-represented (e.g., breast cancer diagnosis, bone density scans) we recommend that you adapt these or other methods to increase enrollment of men. We note that some of these methods may also be adapted to increase enrollment of other typically underrepresented groups, such as racial and ethnic minorities.

[17] We also recommend the provision of race-specific information for each of these bullets to facilitate understanding of difference related to race relevant to the clinical evaluation of your device.

1. For New or Ongoing Studies (IDE study design/early enrollment stage)

You should develop and describe your plan to prospectively enroll proportions of women and men in your study which are consistent with the sex-specific prevalence of the type of disease or condition which your device is intended to treat or diagnose. To enhance enrollment of women, we recommend that you consider the approaches described below.

a. Where appropriate, target investigational sites where recruitment of women can be more easily facilitated (e.g., women's clinics).

b. If women are likely to benefit from your device but may not meet certain study enrollment criteria, consider parallel cohorts for collecting data on device use in women.

c. Plan focused efforts to enroll women under a continued access study.[18]

d. Include provisions to ensure certain minimum enrollment for women (e.g., maintain open enrollment for women until pre-specified proportion is reached).

e. Consider tailored communication strategies (as used in the Women's Health Initiative study)[19] for study recruitment, informed consent documents and patient labeling.

f. Consider factors that increase recruitment such as community or local health care practitioner involvement in recruiting patients, monetary incentives, and presentation of the benefits of participating in the study.

g. Consider flexibility in follow-up visit scheduling with provision of child care or elder care services during appointments.

h. Periodically evaluate screening logs to identify reasons for under-enrollment of women or other key demographic groups, as described in Section III.C.2 above.

2. For Completed Studies (marketing application stage)

If available evidence suggests that there may be clinically significant sex differences in outcomes (related to safety and/or effectiveness) with your device, we recommend that you consider the approaches described below.

[18] CDRH Guidance on IDE Policies and Procedures (1998): http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm.

[19] J. Hays, et al. The Women's Health Initiative Recruitment Methods and Results. *Ann Epidemiol 2003;13:S18–S77.*

a. Plan focused efforts to enroll women under a continued access study.

b. Include provisions to ensure certain minimum enrollment for women (e.g., maintain open enrollment for women until pre-specified proportion is reached).

3. For Postmarket Studies (PAS or 522 PS stage)

You should develop and describe your plan to enroll and retain proportions of women and men in your study which are consistent with the sex-specific prevalence of the type of disease or condition which your device is intended to treat or diagnose. For PAS designed for continued follow-up of the pivotal study cohort, FDA may determine that an additional study of the under-represented sex is warranted. To enhance enrollment of women, we recommend that you consider the approaches described below.

a. Consider whether outstanding questions warrant specific post-market evaluation in women-only studies. For example, this approach may be considered due to sex-specific signals in pre-market clinical studies, or due to known sex differences in the underlying disease or the response to concomitant medication that may impact safety or effectiveness.

b. Where appropriate, target investigational sites where recruitment of needed populations can be more easily facilitated (e.g., women's clinics).

c. Consider tailored communication strategies (as used in the Women's Health Initiative study)[12] for study recruitment, informed consent documents and patient labeling.

d. Consider factors that increase recruitment such as community or local health care practitioner involvement in recruiting patients, monetary incentives, and presentation of the benefits of participating in the study.

e. Consider flexibility in follow-up visit scheduling with provision of child care or elder care services during appointments.

f. Periodically evaluate screening logs to identify reasons for under-enrollment of women or other key demographic groups, as described in Section III.C.2 above.

To minimize loss to follow-up, we recommend you consider the approaches described below, which can assist with avoiding loss-to-follow of subjects regardless of sex.

a. Develop a follow-up plan that details follow-up goals, frequency of contacts, number and type of contact for patients who miss a follow-up visit.

b. Counsel subjects about the importance of returning to follow-up during informed consent and follow-up visits.

c. Collect subjects' contact information and make telephone and written attempts to locate/return patients who miss scheduled clinic visits.

d. Obtain proxy information to use in case unable to contact study subject.

e. Demonstrate interest in subject (e.g., telephone follow-up after surgery, particularly if the device is implantable, send newsletter to subjects to maintain interest).

f. Remind subjects of upcoming scheduled follow-up visits.

g. Ask subjects who withdraw during the study to provide the reason for withdrawal and ask them whether the investigator may contact them once more at the end of the study follow-up to assess the experience with device.

h. Monitor follow-up rates closely so that follow-up problems can be identified and addressed as soon as possible.

i. Report subject accountability data as part of the study report.

V. Recommendations for Sex-Specific Statistical Analysis

Differences between human males and females range from the obvious (e.g., sexual organs, body fat distribution) to the less obvious (e.g., bone density, blood viscosity). Genetic sex can influence all levels of biological organization (cell, organ, organ system, and organism) including susceptibility to disease. Differences between the sexes in the incidence and severity of certain diseases may be related to differences in exposures, routes of entry and processing of a foreign agent, and cellular responses. In addition, differences in health and illness are influenced by an individual's experiences and interaction with the environment, which may be affected by sex.[20] FDA strongly recommends that you investigate and report differences in study outcomes of treatment by sex.

A. Analysis of Effects of Sex on Study Outcomes

After overall effectiveness and safety have been investigated, the influence of sex on primary endpoints for both safety and effectiveness (and in some cases for important secondary endpoints as well) should be assessed. For studies with controls, there may be a substantial difference in how the device performs in females versus males in terms of safety or effectiveness. If such a difference does exist, this is called a treatment-by-sex

[20] Committee on Understanding the Biology of Sex and Gender Differences. *Exploring the Biological Contributions to Human Health: Does Sex Matter?* Institute of Medicine, National Academies of Science. 2001.

interaction effect between sex and the differential effect of the treatment (investigational device) versus the control. If the study is a controlled clinical study, you should plan to investigate the interaction effect between treatment and sex. If the study is a one-arm study without a control group, you should investigate heterogeneity between males and females (i.e., whether the treatment effect is similar or varies by sex.)

It is sometimes helpful to categorize observed treatment by sex or gender interaction as to whether they are qualitative or quantitative interactions. An interaction is said to be *qualitative* if the direction of the treatment effect compared to the control differs between males and females. An interaction is said to be *quantitative* if the directions are the same but the magnitude of the effect differs between males and females.

It may be the case that observed sex differences in clinical outcomes can be explained by other patient characteristics (e.g., body size, co-morbidities, age) that may be correlated with sex. If differences between males and females are observed, we recommend that you investigate whether the differences can be explained by these other patient characteristics.

The recommendations below provide additional details on FDA's preferred method for addressing these potential scenarios.

Subgroup Analysis:

In general, the data should be examined for clinically meaningful sex differences in each of the following, at the primary follow-up time-point, regardless of the potentially limited statistical power of these sex-specific subgroup analyses:

- primary effectiveness endpoint(s);
- primary safety endpoint(s); and
- key secondary endpoints.

Any subgroup analysis (such as the analysis by sex) is usually appropriate only if the overall treatment effect has been established.

Testing for Interaction or Heterogeneity:

For studies with a control group, a statistical test should be performed to evaluate potential interaction between treatment and sex. For one-arm studies with no control group, a test for heterogeneity between males and females should be performed. This type of analysis is currently conducted for the purposes of determining whether data can appropriately be pooled for analysis (e.g., across different sites). The specific methodology could vary; if the methodology requires any assumptions, the validity of these assumptions should be investigated.

- For a primary effectiveness or safety endpoint, if the test for the interaction effect of treatment and sex is statistically significant at an appropriate pre-specified

significance level, this provides strong evidence that the data from both sexes cannot be pooled. In this situation, it can be problematic to make general statements about this endpoint, and so results should be reported separately for each sex. Statistical analysis should also be performed for each sex. If a difference is noted, it is usually helpful to perform additional analyses to investigate possible explanations for this difference using variables such as body size (e.g., body mass index), bone density or concomitant illness (e.g., diabetes). Please note that additional data may be required to appropriately evaluate the effect of sex on the study endpoints; careful consultation with FDA is recommended.

- If a statistically significant interaction is not detected at an appropriate pre-specified significance level, this may suggest that it is valid to pool data in the final analysis. However, your decision about the validity of pooling the data should be based on the size of the observed interaction effect and its clinical importance. It is nonetheless preferable that results be reported by sex.

- In many cases the test for interaction or heterogeneity may have adequate power to detect only a very large interaction (or heterogeneity) effect but may fail to detect a smaller but nevertheless important clinical interaction. In such situations, separate statistical analyses for each sex may be appropriate, and additional data from males or females (or both) may be required. Again, careful consultation with FDA is recommended.

1. For New or Ongoing Studies (IDE study design/early enrollment stage)

The statistical analysis plan in the protocol should include pre-specified plans for addressing the issues described above.

In most cases, the general approach is to plan to test for the overall treatment effect. If the overall treatment effect is not significant, then statistical subgroup analysis by sex is not recommended. However, in the event that the overall treatment effect is significant, then the Statistical Analysis Plan should include an analysis to investigate whether there is any difference between men and women by the interaction test for controlled clinical studies or the test for homogeneity for single arm studies without a control. (If the control is historical and patient-level data exists, then the interaction can be investigated using a propensity score data analysis.) Further, you should make an effort to identify in advance any key additional covariates that might explain possible differences between sexes, and you should pre-specify a model to investigate whether the observed differences can be explained to some extent by these other covariates.

If there is a scientific reason to suspect the existence of a large (or qualitative) interaction effect between sex and treatment, the study may need to be powered to

separately evaluate the treatment effect for each sex. It may be desirable to include sex as a stratification variable; this could allow differential recruitment in males and females. For devices that are appropriate for both men and women, if it is believed that the device is much safer or more effective in one group, we recommend that the study be powered to assess device safety and effectiveness for each sex separately.

It is possible (but rarely done) to plan a study that simultaneously investigates the overall treatment effect and the effect on only one subgroup such as women (or men). This would be done if the claim could be either for the entire population or just one pre-identified sex. This could be accomplished by allocating some fraction *f* of the overall Type I error rate (*alpha*) to the investigation of the overall inferential procedure and the rest to the investigation of the particular subgroup only. In the hypothesis testing framework, the study would then be a success if either the overall test was significant at level *f* times *alpha* or the subgroup was effective at level (*1-f*) times *alpha*.

2. For Completed Studies (marketing application stage)

It is important to carry out all analyses from the Statistical Analysis Plan. If the statistical plans are non-existent or inadequate with respect to sex analyses, you should conduct analyses to evaluate the potential interaction of sex with treatment as described above, and the analyses will be labeled as *post hoc*.

3. For Postmarket Studies (PAS or 522 PS stage)

For PAS involving continuing data collection on PMA cohort patients, we recommend that you conduct the analyses described above for all follow-up time points.

For PAS (or 522 PS studies) involving newly enrolled patients, you should include the analyses above as part of a pre-specified statistical analysis plan in your protocol. Furthermore, if results from sex-specific analyses of pre-market data suggest there may be a clinically meaningful difference in outcomes, you should carefully consult with the Division of Epidemiology to determine whether this should also be incorporated into the study design and hypothesis for your PAS.

When exploring sex-related differences during analysis of data from a PAS or 522 PS study, we recommend you address the issue of confounding by using multivariate analyses adjusted for patient characteristics that may confound the relationship between sex and study outcomes (e.g., smaller size, diabetes, etc.).

B. Interpretation of Sex-Specific Data

If any clinically significant sex differences are found, either based on pre-specified or exploratory *post hoc* analyses, you should discuss with FDA to determine whether additional data are needed to address any remaining sex-specific questions.

If results of your analysis suggest that there is insufficient data to assess whether sex is associated with differences in outcome, FDA may determine that clinical data from additional subjects in one or both sexes may be needed pre- or post-market to address potential sex-specific questions related to safety or effectiveness.

In cases where clinically significant differences between the sexes are observed in safety or effectiveness, FDA may request additional confirmatory studies in one or both sexes, implement specific pre- or post-approval study conditions, and/or modify the design of subsequent studies.

VI. Recommendations for Reporting Sex-Specific Information in Summaries and Labeling

Confidential submissions to FDA contain detailed analyses of clinical study data, which may include a variety of sex-specific analyses. However, public documents on medical devices approved in the past are inconsistent with regard to the degree of information available on device performance in demographic subgroups. Although sponsors may be most interested in the generalizability of the findings, individual patients and their medical providers can benefit from more data regarding effectiveness and potential adverse events associated with device use in a particular demographic subgroup.

A. Enrollment Demographics, Baseline Characteristics & Co-Morbidities

The strength of the conclusions of your clinical study program with respect to device performance in women and men is linked to the representation of each sex in your study(s). FDA recommends that you report the number and proportion of subjects by sex who were treated or diagnosed with your device as part of a clinical study as follows:

- You should report study demographics in terms of proportion enrolled by subgroup. You should discuss whether the proportions enrolled are consistent with the sex-specific prevalence of disease. For studies with multiple arms, you should report enrollment proportions for each sex in each arm.

- If co-morbidities and/or other baseline characteristics are reported, we recommend that you report important baseline characteristics and co-morbidities by demographic subgroup as well as overall.

- For per protocol analyses, we recommend a comparison and discussion of sex-specific differences in follow-up compared to at enrollment, for the overall study sample and for each study arm.

You may choose to adapt the example language below, or you may use similar language which incorporates the contents described above.

Example Language:

Women represented [34%] of the total patients enrolled in the overall study. This is similar to the prevalence of [coronary artery disease] in the general U.S. population [citation]. The proportion of women included in the treatment and control arms did not differ significantly (treatment: 33% vs. control: 34%).

Women were more likely to have diabetes compared to men (35% vs. 22%) and less likely to have prior history of myocardial infarction (24% vs. 36%).

Additionally, we recommend that you include this type of information in any applicable tables and charts.

1. **For New or Ongoing Studies (IDE study design/early enrollment stage)**

   You should report this information as part of your annual progress reports.

2. **For Completed Studies (marketing application stage)**

   You should report this information as part of your marketing application in sections containing results of clinical investigations. A summary of this information should also be included in your draft PMA Summary of Safety and Effectiveness or 510(k) Summary.

3. **For Postmarket Studies (PAS or 522 PS stage)**

   You should report this information in interim reports and in the results section of your final report.

B. Sex-Specific Outcomes (Safety or Effectiveness)

The results of sex-specific outcomes analyses should be presented in the labeling, regardless of whether the analyses are pre-specified or *post hoc*. If analyses suggest a possible sex difference in an endpoint or event with clinical significance, but statistical significance is not reached, you should report the findings descriptively. If results of these analyses suggest no sex differences in outcomes, you should report which analyses were conducted and that no differences were found.

1. **For Completed Studies (marketing application stage)**

   When presenting results of *prespecified* sex analyses, we recommend the following:

   - Clearly state which analyses were conducted
   - Specify statistical methods used to assess for heterogeneity of treatment differences by sex (as described above)
   - You may include inferential statistics, including p-values and/or confidence intervals.

When presenting results of *post hoc* sex-specific analyses, we recommend the following:

- Clearly state that the analyses were unplanned
- Clearly state which analyses were conducted
- Specify statistical methods used to assess for heterogeneity of treatment differences by sex (as described above)
- Use descriptive statistics only (mean, standard deviation, etc.). Results in confidential submissions to PMA can include inferential statistics, with a disclaimer that these are from *post hoc* analyses.

2. For Postmarket Studies (PAS or 522 PS stage)

When presenting results of sex-specific analyses of PAS or 522 PS data, the recommendations above should also apply.

If a clinically significant signal is detected in interim reports, FDA may recommend changes to your previously approved labeling and summaries, to communicate the newly observed sex difference.

If a clinically significant signal is detected in your final analysis, this information should be summarized in your revised labeling which you submit with your final study report.