Evaluation of Sex-Specific and Gender-Specific Data in Medical Device Clinical Studies

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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When final, this guidance will supersede Evaluation of Sex-Specific Data in Medical Device Clinical Studies issued on August 22, 2014.

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

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction[1]

This document provides guidance on the study and evaluation of sex- and/or gender-specific data[2] in clinical investigations or research involving one or more subjects to determine the safety or effectiveness of a device.[3] Upon finalization, this document will update the policy reflected in the existing guidance, "Evaluation of Sex-Specific Data in Medical Device Clinical Studies" by addressing both sex- and gender-specific data and will replace the existing guidance.

The purpose of this guidance is to encourage science-driven consideration of sex and/or gender, as appropriate for both the scientific question being addressed and the intended use of the device, when designing medical device clinical studies and reporting data from such studies in accordance with legal requirements.[4] The guidance provides recommendations for sponsors[5] to

[1] This guidance has been prepared by CDRH in consultation with the Center for Drug Evaluation and Research (CDER) and the Office of Combination Products (OCP).

[2] See section II for detailed definitions of "sex" and "gender" for purposes of this guidance.

[3] 21 CFR 812.3(h) defines "investigation" to mean "a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device." For the purposes of this guidance, the terms *study*, *clinical study*, *trial*, *clinical trial*, and *investigation* refer to a clinical investigation.

[4] The recommendations contained in this guidance are intended to help sponsors meet certain applicable legal requirements. For example, an investigational plan must include a description of the patient population, including sex (see 21 CFR 812.25(c)), and a PMA is required to include information about study population (see 21 CFR 814.20(b)(3)(v)(B), (6)(ii)).

[5] For the for purposes of this guidance, the term *sponsor* includes *investigator* and *sponsor-investigator* unless otherwise noted or apparent from context. See generally 21 CFR 50.3(d)-(f), 812.3(i), (n), (o).

consider sex- and/or gender-specific data throughout the clinical study process. This includes recommendations for clinical study design, study participant[6] enrollment, data collection and analysis, and reporting of study information. The objectives of this guidance are to: 1) encourage the consideration of sex and/or gender during the study design stage, as appropriate for the research hypothesis and the intended use of the device; 2) provide recommendations for study design and conduct to encourage appropriate enrollment by sex and/or gender (e.g., in proportions representative of the demographics of disease distribution, if appropriate); 3) provide recommendations for statistical analyses with a framework for considering sex- and/or gender-specific data when interpreting overall study outcomes; and 4) provide recommendations for reporting sex- and/or gender-specific data to FDA.

In general, FDA's guidance documents 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. Definitions

Use of the term male and female versus man and woman depends upon whether biological or psychosocial factors are under study.[7] For purposes of this document, the terms male and female are used in the context of sex.[8]The terms man, woman, nonbinary and/or transgender[9] are used in the context of gender.[10] In this document, when both sex and gender are relevant to the study, the

[6] FDA acknowledges that its regulations in 21 CFR parts 50, 56, and 812 use the term "subject" or "human subject," (see 21 CFR 50.3(g), 56.102(e), 812.3(p)), but patients may be familiar with a different term. Therefore, in this guidance, the term *study participant* is used instead.

[7] Clayton, J.A. & Tannenbaum, C. (2016). Reporting sex, gender, or both in clinical research? *JAMA 316*(18):1863-1864. Doi:10.1001/jama.2016.16405.

[8] U.S. HHS Implementation Guidance on Data Collection Standards for Race, Ethnicity, Sex, Primary Language, and Disability Status, available at https://aspe.hhs.gov/reports/hhs-implementation-guidance-data-collection-standards-race-ethnicity-sex-primary-language-disability-0. This HHS guidance outlines the minimum data collection standards for race, ethnicity, sex, primary language and disability status for implementation in HHS, among other things. For purposes of the HHS guidance, the minimum data collection standard for sex is male/female. There are no data standards for gender in this HHS guidance.

[9] "Transgender or trans are umbrella terms used to describe people whose gender identities and/or gender expressions are not what is typically expected for the sex to which they were assigned at birth." See Colman, E., Radix, A.E., Bouman, W.P., et al., Standards of Care for the Health Transgender and Gender Diverse People, Version 8 (2022) International Journal of Transgender Health, doi: 10.1080/26895269.2022.2100644. While transgender is generally a good term to use, not everyone whose appearance or behavior is gender-nonconforming will identify as a transgender person. The ways that transgender people are talked about in popular culture, academia and science are changing, particularly as individuals' awareness, knowledge and openness about transgender people and their experiences grow. See American Psychological Association. (2023, March). Psychology Topics, Sexual Orientation and Gender Diversity, Answers to Your Questions About: Understanding Transgender People, Gender Identity and Gender Expression.

[10] For more information, please see National Institutes of Health (NIH) Sex and Gender Minority Research Office, available at https://dpcpsi.nih.gov/sgmro.

terms male/man, female/woman, and/or other participants[11] may be used and such usage indicates male and/or man, female and/or woman, and/or other participants.
While sex and gender are distinct, they are interrelated and are not necessarily mutually exclusive.[12] Sex and gender and their interactions may drive epigenetic influences and resultant physiologic reactions, influence etiology and presentation of disease, and affect treatment outcomes.[13,14]

For the purposes of this guidance:

Sex is a biological construct based on anatomical, physiological, hormonal, and genetic (chromosomal) traits.[15] Sex is generally assigned based on anatomy at birth and is usually categorized as female or male, but variations occur. Variations of sex refers to differences in sex development (DSD) or intersex traits.[16,17]

Gender is a multidimensional construct that encompasses how an individual self-identifies.[18] Gender may be described across a continuum, may be nonbinary, and may change over the course of a lifetime. Gender may or may not correspond to a person's sex assigned at birth.[19]

III. Background

There has been a steadily growing recognition of the importance of sex- and gender-specific considerations in areas such as medical technology design and development, including clinical study design, and assessing product performance throughout the total product life cycle and other medical device-related matters. Since the 2001 Institute of Medicine consensus report[20] there has been advancement in basic science research and the development of clinical data that demonstrates the premise that sex is a basic biological variable and that every cell has a sex.[21]

[11] The term "other participants" is intended to allow for inclusion of intersex individuals as well as those with non-binary or fluid gender identities.
[12] National Academies of Sciences, Engineering, and Medicine. 2022. Measuring Sex, Gender Identity, and Sexual Orientation. Washington, DC: The National Academies Press.
[13] See Footnote 12.
[14] Cornelison, T. L., & Clayton, J. A. (2017). Considering sex as a biological variable in biomedical research. *Gender and the Genome, 1*(2), 89-93.
[15] See Footnote 12.
[16] See Footnote 12.
[17] Clinical studies may include a category for "intersex" to collect data on individuals whose chromosomal, gonadal, or anatomic sex is atypical. Further discussion of intersex variations is beyond the scope of this guidance.
[18] See Footnote 12.
[19] See Footnote 12.
[20] *Institute of Medicine. Exploring the Biological Contributions to Human Health: Does Sex Matter?* (2001). In T. M. Wizemann & M.-L. Pardue (Eds.).
[21] See Footnote 14.

Sex and gender are key considerations in the development and performance of medical devices.[22] The expression of an individual's gender may be influenced by social and cultural expectations about status, characteristics, and behavior as they are associated with certain sex traits.[23] Gender also plays an important role in human health and disease.[24] There are differences associated with gender in various areas such as mental health, pain assessment and management, clinical outcomes, and health care utilization.[25,26,27,28] As more sex- and gender-specific data are accessible, innovators and other stakeholders will better comprehend how to study the interaction of sex with gender,[29] and continue to identify possible sex- and gender-specific differences that are relevant throughout the total product life cycle.

Though there has been steady growth in the recognition of sex- and gender-considerations in medical technology design and development, it is important to understand that this was not always the case. Historically, females/women have been under-represented in or excluded from many clinical studies. This has led to a lack of information available for females/women and their health care providers regarding the benefits and risks of many medical devices. Further, individuals with intersex traits and those with differences in sex development may have not been properly included within clinical studies. In addition, historically, as gender was often conflated with sex or otherwise not properly reported in clinical studies, there is a lack of data regarding the underrepresentation of nonbinary, transgender, fluid gender identities and other gender identities. Over recent decades, there has been an increase in the representation of females/women in clinical studies with greater availability of sex- and gender-specific data,[30] including in medical device data, yet females/women remain under-represented in some therapeutic areas.[31] Consideration of gender in medical technology design and development is

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[22] Miller, V. M., Rice, M., Schiebinger, L., Jenkins, M. R., Werbinski, J., Nunez, A., . . . Shuster, L. T. (2013). Embedding concepts of sex and gender health differences into medical curricula. *J Womens Health (Larchmt), 22*(3), 194-202. doi:10.1089/jwh.2012.4193.

[23] See National Institutes of Health, Office of Research on Women's Health website on Sex and Gender, available at https://orwh.od.nih.gov/sex-gender.

[24] World Health Organization. (2021, May). Newsroom, Questions and Answers, Gender and Health: *How Do Sex and Gender Influence Health?*

[25] Safdar, B., & Greenberg, M. R. (2014). Applying the gender lens to emergency care: from bench to bedside. *Acad Emerg Med, 21*(12), 1325-1328. doi:10.1111/acem.12521.

[26] Greenberg, M. R., Safdar, B., Choo, E. K., McGregor, A. J., Becker, L. B., & Cone, D. C. (2014). Future directions in sex- and Gender-specific Emergency Medicine. *Acad Emerg Med, 21*(12), 1339-1342. doi:10.1111/acem.12520.

[27] Ranney, M. L., Locci, N., Adams, E. J., Betz, M., Burmeister, D. B., Corbin, T., . . . Houry, D. E. (2014). Gender-specific research on mental illness in the emergency department: current knowledge and future directions. *Acad Emerg Med, 21*(12), 1395-1402. doi:10.1111/acem.12524.

[28] Musey, P. I., Jr., Linnstaedt, S. D., Platts-Mills, T. F., Miner, J. R., Bortsov, A. V., Safdar, B., . . . McLean, S. A. (2014). Gender differences in acute and chronic pain in the emergency department: results of the 2014 Academic Emergency Medicine consensus conference pain section. *Acad Emerg Med, 21*(12), 1421-1430. doi:10.1111/acem.12529.

[29] See Footnote 14.

[30] See e.g., Executive Order 14120, Advancing Women's Health Research and Innovation (89 FR 20095, March 18, 2024).

[31] Gong IY, Tan NS, Ali SH, Lebovic G, Mamdani M, Goodman SG, Ko DT, Laupacis A, Yan AT. (2019). Temporal trends of women enrollment in major cardiovascular randomized clinical trials. *Can J Cardiol, 35*(5), 653-660. doi: 10.1016/j.cjca.2019.01.010. Epub 2019 Jan 30.

necessary to help improve the generalizability of research results to all intended patient populations, including women, nonbinary people, transgender people, people with fluid gender identities, and people with other gender identities that historically have been underrepresented.

In addition to a lack of available data for females/women in clinical studies, females/women may be less likely than males/men to enroll in clinical studies, for various reasons. Some of the reasons include, but are not limited to:[32,33,34,-35] sponsors may not give females/women as many opportunities to participate in clinical research; female/women prospective participants may be concerned about the risk of adverse fetal or fertility consequences if they desire future pregnancy, are pregnant, or become pregnant (e.g., effects of radiographic assessments or concomitant drug therapy) during a clinical study, or certain information to assess such risks may not be known; potential female/women participants generally may have more family responsibilities, limiting their ability to commit time to a clinical study, including follow-up; or sponsors may establish inclusion/exclusion selection criteria that unintentionally exclude females/women.

To help ensure devices are safe and effective for their intended use, it is important that a medical device be developed and evaluated with study participants that represent the demographic, clinical, and disease characteristics of the intended population. Accordingly, given the historical concerns and the growing recognition of the importance of sex- and gender-specific considerations in medical technology design and development, this guidance focuses on recommendations that help ensure that sex- and/or gender are adequately considered as a medical device clinical study is designed and conducted, and resulting data are analyzed. Whether a sponsor will collect and analyze both sex-specific and gender-specific data, or data related to just one of these specific traits, is dependent upon the scientific question being addressed and the intended use of the product.

IV. Scope

This guidance is intended for sponsors that submit clinical information in support of a premarket submission for a device, whether a premarket notification (510(k)), premarket approval (PMA) application, a De Novo classification request, humanitarian device exemption (HDE) application, biologics license application (BLA), or investigational device exemption (IDE) application.

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[32] See Department of Health and Human Services, Food and Drug Administration, Report to Congress, September 2009, "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 at https://www.fda.gov/regulatory-information/food-and-drug-administration-amendments-act-fdaaa-2007/fdaaa-implementation-chart.

[33] Liu KA, Dipietro Mager NA. (2016). Women's involvement in clinical trials: historical perspective and future implications. *Pharm Pract* 14(1), 708. doi: 10.18549/PharmPract.2016.01.708.

[34] Myles S, Tocci C, Falk M, Lynch S, Torres C, Brown B, Firman BL, Lake M, Maser CA, Onativia A, Obermeier EM, Macfarlan J, Wapner R, Smulian JC, Kurt A. (2018). A multicenter investigation of factors influencing women's participation in clinical trials. J Womens Health 27(3), 258-270. DOI: 10.1089/jwh.2017.6458.

[35] See FDA guidance document Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry.

Certain devices subject to premarket review through a BLA under section 351 of the Public Health Service Act are studied under an investigational new drug application (IND). While this guidance focuses on clinical investigations subject to the IDE regulations in 21 CFR Part 812, the recommendations it provides may also be relevant to consider for device investigations conducted under an IND. The recommendations contained herein also apply to post-approval studies (PAS) required by FDA as condition of approval and postmarket surveillance (PS) clinical studies conducted in accordance with section 522 of the Federal Food, Drug, and Cosmetic (FD&C) Act, where noted.

FDA recognizes that many medical device clinical studies designed to evaluate biological factors (sex) rely on study participant self-reported values that may reflect gender. This guidance provides recommendations for sponsors to consider in the design, conduct, analysis, and interpretation of medical device clinical studies to ensure sex and gender are appropriately considered.

Sex and gender are not the only characteristics that may affect device performance. While this guidance focuses on considerations relating to sex and gender, the recommendations discussed in this guidance may also be applied to promote study enrollment and data analysis adequately accounting for other variables, such as age,[36] race,[37] and ethnicity.[38,39] In general, a medical device should be developed and validated in clinical studies involving study participants that represent the demographic, clinical, and disease characteristics of the intended population.

The impact of sex and/or gender may be more relevant to certain types of products or diseases than others. For example, certain obstetrical, gynecologic and urologic devices may be intended for use in single-sex populations, so clinical studies of these devices would not be expected to address the potential for sex-specific outcomes. Even for these devices, however, there may be important gender-based differences that should be considered, such as device performance in

[36] For more information on pediatric populations, please see FDA draft guidance document Ethical Considerations for Clinical Investigations of Medical Products Involving Children. When finalized this guidance will provide FDA's current thinking on the topic.

[37] Statistical Policy Directive No. 15, as revised (SPD 15), published by the Office of Management and Budget (OMB), "provides the standards for maintaining, collecting, and presenting race and ethnicity data for all Federal information collection and reporting purposes." Revisions to OMB's Statistical Policy Directive No. 15: Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity, 89 Fed. Reg. 22182, 22191 (March 29, 2024).. Per OMB, the "categories in these standards are understood to be socio-political constructs and are not an attempt to define race and ethnicity biologically or genetically." *Id.* For this reason, the term race is used in this document even in the context of genetic ancestry. It is recognized that race is not necessarily a scientifically or anthropologically accurate surrogate for genetic ancestry, but it is self-reported by participants in clinical studies, Sirugo G, Tishkoff SA, Williams SM. (2021). The quagmire of race, genetic ancestry, and health disparities. *J Clin Invest, 131*(11):e150255. doi: 10.1172/JCI150255. PMID: 34060479; PMCID: PMC8159696.].

[38] See FDA guidance document Collection of Race and Ethnicity Data in Clinical Trials. (FDA issued a draft guidance entitled "Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products" on January 30, 2024. When finalized, the Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products guidance will replace the Collection of Race and Ethnicity Data in Clinical Trials guidance.)

[39] See FDA guidance document Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies.

transgender men who choose to retain their uterus/ovaries (e.g., to maintain the option of pregnancy). While the guidance discusses both sex and gender, the scientific question being addressed and intended use of the device drives the inclusion of these data, whether both sex-specific and gender-specific data, or one or the other.

FDA recommends the use of this guidance document as a supplement to other FDA guidance, in particular, any relevant device-specific guidance or cross-cutting guidance pertaining to aspects of a clinical study. For device-specific questions, consultation with the appropriate FDA review division is advised.

V. Why Consider Sex- and Gender-Specific Differences?

Certain medical products elicit different responses depending on a person's sex, gender, or both. 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 vary by sex, gender, age, race, or ethnicity and these factors should be considered in study recruitment and in reporting of results. Additionally, differences in patient-reported outcomes between certain groups, for example how males/men and females/women report pain differently,[40] may suggest a sex- and/or gender -specific difference in outcome, but this difference may not necessarily be related to the medical device itself.

Covariates associated with female sex (e.g., body size, age, co-morbidities, past pregnancies, current pregnancy state) may be responsible for certain differences in device safety, effectiveness, or design attributes such as failure mode. 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 hormone-mediated differences in metabolism or changes in fluid balance, which could lead to intra-subject variability. Covariates that may be associated with gender include how one interprets pain and disability, and when someone accesses the health care system. As the science in this area is still developing, there may be other covariates not discussed within this document that may be associated with sex and or gender.

The following are some examples of health conditions where sex- and/or gender-specific differences may affect the device's performance and corresponding clinical outcomes.

- In the cardiovascular system, sex-based differences are observed in clinical outcomes with different medical device types. With left ventricular assist devices, females have a higher risk for right ventricular failure, stroke, other neurologic complications,

[40] Osbourne, N. R., Davis, K. D. (2022). Sex and gender differences in pain. Int Rev Neurobiol, 164:227-307. doi: 10.1016/bs.irn.2022.06.013.

arrhythmias, bleeding, and thrombosis.[41- 47] Females are also more likely than males to have complications from implantable cardioverter-type defibrillators.[48]

- In orthopedics, implanted devices are affected by sex. Females have an increased risk of knee osteoarthritis than males, with greater severity at presentation.[49,50] More females have total knee replacement surgery than men in the United States, and are three times

[41] Birks, E. J., McGee, E. C., Jr., Aaronson, K. D., Boyce, S., Cotts, W. G., Najjar, S. S., . . . Investigators, A. T. (2015). An examination of survival by sex and race in the HeartWare Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) Bridge to Transplant (BTT) and continued access protocol trials. *J Heart Lung Transplant, 34*(6), 815-824. doi:10.1016/j.healun.2014.12.011.

[42] Weymann, A., Patil, N. P., Sabashnikov, A., Mohite, P. N., Garcia Saez, D., Amrani, M., . . . Simon, A. R. (2015). Gender differences in continuous-flow left ventricular assist device therapy as a bridge to transplantation: a risk-adjusted comparison using a propensity score-matching analysis. *Artif Organs, 39*(3), 212-219. doi:10.1111/aor.12361.

[43] Morris, A. A., Pekarek, A., Wittersheim, K., Cole, R. T., Gupta, D., Nguyen, D., . . . Vega, J. D. (2015). Gender differences in the risk of stroke during support with continuous-flow left ventricular assist device. *J Heart Lung Transplant, 34*(12), 1570-1577. doi:10.1016/j.healun.2015.08.013.

[44] Sherazi, S., Kutyifa, V., McNitt, S., Papernov, A., Hallinan, W., Chen, L., . . . Alexis, J. D. (2017). Effect of Gender on the Risk of Neurologic Events and Subsequent Outcomes in Patients With Left Ventricular Assist Devices. *Am J Cardiol, 119*(2), 297-301. doi:10.1016/j.amjcard.2016.09.032.

[45] Hsich, E. M., Naftel, D. C., Myers, S. L., Gorodeski, E. Z., Grady, K. L., Schmuhl, D., . . . Young, J. B. (2012). Should women receive left ventricular assist device support?: findings from INTERMACS. *Circ Heart Fail, 5*(2), 234-240. doi:10.1161/CIRCHEARTFAILURE.111.963272.

[46] Magnussen, C., Bernhardt, A. M., Ojeda, F. M., Wagner, F. M., Gummert, J., de By, T., . . . Reichenspurner, H. (2018). Gender differences and outcomes in left ventricular assist device support: The European Registry for Patients with Mechanical Circulatory Support. *J Heart Lung Transplant, 37*(1), 61-70. doi:10.1016/j.healun.2017.06.016.

[47] Starling, R. C., Naka, Y., Boyle, A. J., Gonzalez-Stawinski, G., John, R., Jorde, U., . . . Pagani, F. D. (2011). Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol, 57*(19), 1890-1898. doi:10.1016/j.jacc.2010.10.062.

[48] Peterson, P. N., Daugherty, S. L., Wang, Y., Vidaillet, H. J., Heidenreich, P. A., Curtis, J. P., . . . National Cardiovascular Data, R. (2009). Gender differences in procedure-related adverse events in patients receiving implantable cardioverter-defibrillator therapy. *Circulation, 119*(8), 1078-1084. doi:10.1161/CIRCULATIONAHA.108.793463.

[49] Lim, J. B., Chi, C. H., Lo, L. E., Lo, W. T., Chia, S. L., Yeo, S. J., . . . Lo, N. N. (2015). Gender difference in outcome after total knee replacement. *J Orthop Surg (Hong Kong), 23*(2), 194-197. doi:10.1177/230949901502300216.

[50] Srikanth, V. K., Fryer, J. L., Zhai, G., Winzenberg, T. M., Hosmer, D., & Jones, G. (2005). A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage, 13*(9), 769-781. doi:10.1016/j.joca.2005.04.014.

more likely than males to undergo total knee replacement at a more advanced stage.[51- 56] However, even though females achieve greater improvement in pain and function outcome relative to pre-operative state, females do not reach the same benefit levels of males in final outcome.[57,58]

- There are sex-based differences in diagnostic imaging testing patterns. The focus of cardiac imaging for female patients is changing from an anatomy-based coronary artery disease assessment to a more physiologic-based ischemic heart disease analysis.[59,60] The reason for this shift is that female patients experience microvascular cardiac disease more often than males, primarily in the precapillary coronary arterioles.[61] As a result, imaging limited to epicardial artery anatomy may be less useful in female than in male

[51] See Footnote 49.
[52] See Footnote 50.
[53] Hawker, G. A., Wright, J. G., Coyte, P. C., Williams, J. I., Harvey, B., Glazier, R., & Badley, E. M. (2000). Differences between men and women in the rate of use of hip and knee arthroplasty. *N Engl J Med, 342*(14), 1016-1022. doi:10.1056/NEJM200004063421405.
[54] Katz, J. N., Wright, E. A., Guadagnoli, E., Liang, M. H., Karlson, E. W., & Cleary, P. D. (1994). Differences between men and women undergoing major orthopedic surgery for degenerative arthritis. *Arthritis Rheum, 37*(5), 687-694.
[55] Petterson, S. C., Raisis, L., Bodenstab, A., & Snyder-Mackler, L. (2007). Disease-specific gender differences among total knee arthroplasty candidates. *J Bone Joint Surg Am, 89*(11), 2327-2333. doi:10.2106/JBJS.F.01144.
[56] Maradit Kremers, H., Larson, D. R., Crowson, C. S., Kremers, W. K., Washington, R. E., Steiner, C. A., . . . Berry, D. J. (2015). Prevalence of Total Hip and Knee Replacement in the United States. *J Bone Joint Surg Am, 97*(17), 1386-1397. doi:10.2106/JBJS.N.01141.
[57] See Footnote 49.
[58] Lavernia, C., D'Apuzzo, M., Rossi, M. D., & Lee, D. (2009). Is postoperative function after hip or knee arthroplasty influenced by preoperative functional levels? *J Arthroplasty, 24*(7), 1033-1043. doi:10.1016/j.arth.2008.09.010.
[59] Safdar, B., Nagurney, J. T., Anise, A., DeVon, H. A., D'Onofrio, G., Hess, E. P., . . . Diercks, D. B. (2014). Gender-specific research for emergency diagnosis and management of ischemic heart disease: proceedings from the 2014 Academic Emergency Medicine Consensus Conference Cardiovascular Research Workgroup. *Acad Emerg Med, 21*(12), 1350-1360. doi:10.1111/acem.12527.
[60] Mieres JH, S. L., Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS, Wenger NK; Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. (2005). Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation, 111*(5), 682-696. doi:10.1161/01.CIR.0000155233.67287.60.
[61] von Mering, G. O., Arant, C. B., Wessel, T. R., McGorray, S. P., Bairey Merz, C. N., Sharaf, B. L., . . . Blood, I. (2004). Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation, 109*(6), 722-725. doi:10.1161/01.CIR.0000115525.92645.16.

patients.[62] In contrast, diagnostic measurements of cardiac perfusion, microcirculatory resistance, and coronary flow reserve may be more beneficial in female patients.[63-66]

- Over the years, there has been much research about gender-based differences related to pain experiences and analgesic effects.[67,68] In population-based research, women consistently experience more severe acute and chronic pain across a range of conditions than men.[69-71] Wide variation in individual responses to opioid medications, due to underlying physiologic, genetic and hormonal determinants of the response, has made it challenging to detect gender differences in clinical response.[72] Nevertheless, it has been shown that there are gender-based differences in pain severity perceptions.[73]

For more information on sex- and/or gender-specific differences and their impact on health conditions, please see the CDRH Health of Women Strategic Plan.

VI. Clinical Studies Considerations

This guidance provides recommendations for the consideration and evaluation of sex- and/or gender-specific data for medical device clinical studies (premarket and postmarket) through all phases of study development including development of the scientific rationale and study design, enrollment of study participants, data collection, analysis and interpretation, as well as inclusion

[62] Yiu, K. H., de Graaf, F. R., Schuijf, J. D., van Werkhoven, J. M., Marsan, N. A., Veltman, C. E., . . . Jukema, J. W. (2012). Age- and gender-specific differences in the prognostic value of CT coronary angiography. *Heart, 98*(3), 232-237. doi:10.1136/heartjnl-2011-300038.

[63] Kern, M. J., Lerman, A., Bech, J. W., De Bruyne, B., Eeckhout, E., Fearon, W. F., . . . Interventional Cardiac Catheterization, C. o. C. C. (2006). Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. *Circulation, 114*(12), 1321-1341. doi:10.1161/CIRCULATIONAHA.106.177276.

[64] Ng, M. K., Yeung, A. C., & Fearon, W. F. (2006). Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance compared with coronary flow reserve. *Circulation, 113*(17), 2054-2061. doi:10.1161/CIRCULATIONAHA.105.603522.

[65] Gulati, M., Shaw, L. J., & Bairey Merz, C. N. (2012). Myocardial ischemia in women: lessons from the NHLBI WISE study. *Clin Cardiol, 35*(3), 141-148. doi:10.1002/clc.21966.

[66] Safdar, B., Lichtman, J. H., & D'Onofrio, G. (2012). Sex and the CT: an evolving story of the heart. *Acad Emerg Med, 19*(2), 197-200. doi:10.1111/j.1553-2712.2011.01288.x.

[67] Fillingim, R. B., & Gear, R. W. (2004). Sex differences in opioid analgesia: clinical and experimental findings. Eur J Pain, 8(5), 413-425. doi:10.1016/j.ejpain.2004.01.007.

[68] Fillingim, R. B., Ness, T. J., Glover, T. L., Campbell, C. M., Hastie, B. A., Price, D. D., & Staud, R. (2005). Morphine responses and experimental pain: sex differences in side effects and cardiovascular responses but not analgesia. *J Pain, 6*(2), 116-124. doi:10.1016/j.jpain.2004.11.005.

[69] Leresche, L. (2011). Defining gender disparities in pain management. *Clin Orthop Relat Res, 469*(7), 1871-1877. doi:10.1007/s11999-010-1759-9.

[70] Riley, J. L., 3rd, Robinson, M. E., Wise, E. A., Myers, C. D., & Fillingim, R. B. (1998). Sex differences in the perception of noxious experimental stimuli: a meta-analysis. *Pain, 74*(2-3), 181-187.

[71] Bingefors, K., & Isacson, D. (2004). Epidemiology, co-morbidity, and impact on health-related quality of life of self-reported headache and musculoskeletal pain--a gender perspective. *Eur J Pain, 8*(5), 435-450. doi:10.1016/j.ejpain.2004.01.005.

[72] See Footnote 28.

[73] See Footnote 28.

of sex- and/or gender-specific information from clinical studies in premarket submissions and device labeling.

A. Considerations for Development of the Scientific Rationale and Study Design

Differences between males and females range from the more apparent (e.g., sexual organs, body fat distribution) to the less apparent (e.g., bone density, blood viscosity). Sex can affect all levels of biological organization (cell, organ, organ system, and organism), including susceptibility to disease. Both sex and gender and their interactions may induce epigenetic events and resultant physiological cascades.[74] Differences across the sexes and genders 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 and/or gender.[75] Considering sex and gender at the beginning of the research allows for the study to be designed in a way that permits sponsors to discern possible unanticipated differences between subgroups. Data viewed in an aggregated form may lead to a perceived conclusion that a device had no effect or that a pathway had no relevance for the disease. For example, considering male data only may prompt a conclusion that contradicts observed results in females. This type of perceived conclusion has been seen in the models of ischemic stroke, where the pathway was previously well established in models with male mice only, but female mice showed the exact opposite pattern. Specifically, a selective PARP-1 inhibitor reduced total infarction in male mice but increased ischemic damage in female mice.[76] Sex and gender differences play significant roles in various areas of treatment and preventive interventions. Therefore, unless the device is intended for use in only one sex (e.g., prostate-specific antigen testing for prostate cancer) or one gender, it is important that the variation in data across sex and/or gender be considered from the beginning as part of the scientific rationale utilized to develop and design the clinical study to determine the safety or effectiveness of the medical device for its intended use.

After framing the scientific rationale, sponsors should then consider how sex- and gender-differences may impact the study design. Clinical studies should be designed to include representative populations that reflect the intended use population for the device. In general, to achieve an unbiased estimate of treatment effect in the general population, sponsors should plan to enroll representative proportions of study participants (e.g., consistent with disease prevalence). However, in cases where disease science or prior clinical study results suggest treatment effect in only one sex and/or gender, sponsors may need to design the study to appropriately analyze the intended use of the device and intentionally enroll sufficient numbers to power the study (i.e., a sample size sufficient for sex- and/or gender-specific intended uses).

[74] See the CDRH Health of Women Strategic Plan.

[75] See Footnote 20.

[76] McCullough LD, Zeng Z, Blizzard KK, Debchoudhury I, Hurn PD. Ischemic nitric oxide and poly (ADP-ribose) polymerase-1 in cerebral ischemia: male toxicity, female protection. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism. 2005;25(4):502-512.

To understand potential sex- and/or gender-specific differences that may be relevant to the clinical evaluation of the device, FDA recommends that sponsors investigate whether sex- and/or gender-specific differences exist for the effect that the device is intended to have, or disease or condition that the device is intended to cure, treat, diagnose, mitigate, or prevent, in the following areas:[77]

- sex- and/or gender-specific prevalence
- sex- and/or gender-specific diagnosis and treatment patterns
- limited clinical evidence due to disproportionately low number of females/women included in prior studies for the target indication
- identification of any known clinically meaningful sex- and/or gender-specific differences in outcomes related to either safety or effectiveness

If information demonstrating sex- and/or gender-specific differences is available, whether based on previous studies, literature, or disease science, it should be included in the study and submission documents as described in the following sections. FDA recognizes that such information is limited in some device development programs (e.g., those based on testing conducted with specimens that are not individually identifiable), but FDA generally recommends sponsors provide whatever information is available regarding sex and/or gender.

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

Sponsors should include the information considering sex- and/or gender-specific differences described above as part of the risk analysis section of the investigational plan (see 21 CFR 812.25(c)). FDA also recommends that sponsors summarize this information in the investigator training materials to explain, and that the study protocol reflect, the importance of enrolling appropriate proportions of study participants. For studies that are already enrolling under an approved (or approved with conditions) IDE where enrollment of men, women, or other study participants is not adequate and where clinically meaningful sex- and/or gender-specific differences are suspected, the sponsor should discuss with FDA plans to increase enrollment of under-represented groups without compromising data integrity, for example, due to implementing changes to an in-progress study.

(2) For Completed Premarket Studies (premarket submission stage)

Where previous studies, literature, or disease science suggest there are clinically meaningful sex- and/or gender-specific differences, sponsors should include this information as part of the premarket submission in sections containing results of clinical studies. A summary of this information should also be included in any draft PMA Summary of Safety and Effectiveness, 510(k) Summary, HDE Summary of Safety and Probable Benefit, De Novo Summary documents the sponsor submits, and in the labeling (see Section VI.D below for more details).

[77] The intent of this recommendation is to provide context based on disease science. Sponsors may consider providing similar information related to other demographic groups such as age, race, ethnicity, co-morbidities, etc.

(3) For Postmarket Clinical Studies (Post-approval Studies (PAS) or Section 522 Postmarket Surveillance (PS) stage)

Where previous studies, literature, or disease science suggest there are clinically meaningful sex- and/or gender-specific differences, sponsors should include this information on the study population in interim reports and in the results section of the final report.[78] If warranted, sponsors should also submit revised labeling to include this information.

B. Recommendations for Achieving Representative Enrollment and Retention

(1) Enrollment and Retention for New Clinical Studies

As discussed, females/women, including pregnant individuals, have been historically under-represented in clinical studies of medical devices; therefore, the approaches described below are generally described as useful for increasing enrollment of females/women in clinical studies to improve generalizability of research results to intended patient populations. However, in fields where men may be under-represented (e.g., breast cancer diagnosis, bone density scans), FDA similarly recommends that sponsors adapt these or other methods to increase enrollment of men if the intended population also includes males/men. Some of these methods may also be adapted to increase enrollment of other typically under-represented groups, such as groups based on age, race and ethnicity.[79] Sponsors should develop and describe their plan to enroll and retain proportions of study participants in the study that are consistent with the sex- and/or gender-specific prevalence of the type of disease or condition that the device is intended to treat or diagnose.[80] Some strategies that sponsors may consider to increase enrollment and retention within clinical studies include:

- Target investigational sites where recruitment of females/women and/or other under-represented participants can be more easily facilitated (e.g., women's clinics, sex and gender minority-based clinics).
- Consider expanded communication strategies, such as community presentations and alliance building with area women's groups (as used in the Women's Health Initiative study[81]), for study recruitment.[82]

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[78] For more information on PAS, please see FDA guidance Procedures for Handling Post-Approval Studies Imposed by PMA Order. For more information on Section 522 Postmarket Surveillance, please see FDA guidance Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act,.

[79] For broader approaches on enhancing clinical trial diversity, see Footnotes 31 and 35.

[80] Sponsors may be required to develop or submit information regarding the representativeness of clinical study participants. For example, the FD&C Act, as amended by section 3601(b) of the Food and Drug Omnibus Reform Act of 2022 (FDORA), enacted as part of the Consolidated Appropriations Act, 2023 (P.L. 117-328)), will require sponsors to submit to FDA diversity action plans for studies of certain devices. *See* FD&C Act sec. 520(g)(9), 21 U.S.C. § 360j(g)(9).

[81] Hays, J., Hunt, J. R., Hubbell, F. A., Anderson G. L., Limacher, M., Allen, C., Rossouw, J.E. (2003). The Women's Health Initiative recruitment methods and results. *Ann Epidemiol, 13*(9 Suppl), S18–S77. doi: 10.1016/s1047-2797(03)00042-5.

[82] For more information on patient engagement activities that may enhance the design and conduct of clinical studies please see FDA guidance Patient Engagement in the Design and Conduct of Medical Device Clinical Studies.

- If females/women and/or other underrepresented participants are likely to benefit from the device but may not meet certain study enrollment criteria, consider revising the enrollment criteria, when appropriate, or consider parallel cohorts for collecting data on device use in females/women and/or other underrepresented participants.
- Include voluntary provisions to encourage enrollment of females/women and/or other under-represented participants in numbers that are sufficient for the scientific question being addressed and the intended use of the device.
- Investigate reasons for under-enrollment or non-enrollment of females/women or other key demographic groups (e.g., periodically evaluate screening logs for all study participants who are screened but not ultimately enrolled in studies).
- Consider factors that generally increase recruitment and retention such as community or local health care provider involvement in recruiting or referring study participants, compensation and reimbursement[83] (e.g., for transportation costs), or providing updated information about the status of the study as appropriate (e.g., send a newsletter to study participants to maintain interest).
- Consider flexibility in follow-up visit scheduling that allows various opportunities to accommodate study participants' schedules, which may include evenings and weekends with provision of childcare or elder care services during appointments.
- For in vitro diagnostics and other diagnostic devices, include samples from males/men, females/women and/or other study participants, at the cutoff selection and validation stages.
- Enroll female participants of child-bearing age and pregnant individuals with appropriate risk reduction if pregnancy is contraindicated during study participation.
- If enrolling pregnant individuals, consider the incidence of the condition being treated, the severity of the condition, and the availability of other therapeutic options and their risks. In general, early phase clinical studies in a nonpregnant population should be completed before enrolling pregnant individuals in later phase clinical studies.
- To improve the ability to obtain information about pharmacokinetics in pregnant participants, consider, where applicable, pharmacokinetic sampling during the trial and also prior to dropout, if it occurs. Collecting this type of data improves the ability to inform the instructions for use.

FDA also recommends that sponsors and clinical study investigators consider the approaches described below, which can help avoid or minimize loss-to-follow up of study participants (regardless of sex and/or gender).

Recommended Sponsor Activities

- Develop a follow-up plan including follow-up goals, frequency of contacts, and number and type of contact for study participants missing a follow-up visit.
- Monitor follow-up rates closely so that challenges in achieving sufficient follow-up can be identified and addressed as soon as practicable.

[83] For more information, please see FDA information sheet on Payment and Reimbursement to Research Subjects.

- Report study participant accountability data as part of the study report.

Recommended Clinical Study Investigator(s) Activities

- As part of the informed consent process, counsel study participants about the importance of returning for follow-up visits, while providing study participants with the information required under 21 CFR 50.25, including that they may discontinue participation in the study at any time without losing benefits to which they are otherwise entitled.
- Remind study participants of upcoming scheduled follow-up visits.
- Attempt to locate/reschedule/re-engage study participants who miss scheduled follow-up visits.
- Obtain contact information for multiple contact methods (e.g., both email and cell phone number) when appropriate to use when unable to contact a study participant through a single method.
- Ask study participants who withdraw during the study (or their legally authorized representatives) to provide the reason for withdrawal and, if included in the study protocol, ask them whether the investigator may contact them at the end of the study to assess the experience with device.

(2) Enrollment for Ongoing Clinical Studies

Where ongoing enrollment data demonstrate an under-representation of a particular sex and/or gender enrolling in the study, sponsors are encouraged to investigate the reason for lack of enrollment and consider the approaches to enhance enrollment. It may be informative to evaluate whether the demographic distribution varies at different key time points (e.g., at screening, evaluation of study inclusion/exclusion criteria, consent, and at various follow-up time points). For example, if the proportion of females/women drops significantly after screening for eligibility criteria, this may suggest that the study criteria may need to be examined to reduce any inappropriate, unintentional exclusion of females/women. For example, cutoffs excluding study participants with smaller body surface area may exclude large proportions of female/women participants who may be appropriate for a study of the investigational device. Removing or modifying such exclusions (entirely or through parallel cohort studies) could improve the participation rates of females/women in the overall study. Information regarding changes in demographic distribution at the aforementioned key time points can provide insight into methods that may substantially lower barriers to enrollment of females/women, as well as other subgroups of study participants. These considerations may include flexibility in retention efforts such as scheduling follow-up visits for those who need to plan for childcare or elder care services during appointments. If prespecified targeted enrollment for females/women and/or other under-represented participants is not met, consider focused efforts to enroll the under-accrued population(s) in a supplemental study. Changes to a study protocol and informed consent can be made based on demographic distribution information with appropriate notification to and approval from the IRB and, where necessary, FDA.[84] However, whenever significant changes are made to the protocol mid-study, an assessment of the potential impact to data integrity, analysis, and interpretation should be conducted.

[84] See 21 CFR 50.27, 56.108(a)(3)-(4), 56.111, 812.35.

C. Considering Sex and/or Gender in Data Collection, Analysis, and Interpretation

Collecting sex and/or gender data in a standardized manner and analyzing data disaggregated by sex and/or gender may improve data quality and enable better data interpretation. When subgroup data are analyzed in aggregate, differences between subgroups may be masked.

As previously noted, it is recognized that most medical device clinical studies rely on participant self-reported values even when the study is designed to evaluate biological factors. At present, there are no universally agreed-upon validated tools for collecting gender-related data within the scientific community. One approach may be to ask study participants for both their sex assigned at birth and their current gender identity.[85,86]

(1) Statistical Concepts for Assessing Heterogeneity Across Sex and/or Gender Groups

There may be a substantial difference in how a device performs in different study participants in terms of safety or effectiveness. Thorough investigation of heterogeneity across sex and/or gender groups, especially for primary safety and effectiveness endpoints, should be conducted. Heterogeneity here refers to a difference in a treatment effect on an outcome across sexes and/or genders. Statistical hypothesis tests can be performed to detect heterogeneity, and methods of statistical inference for estimating its magnitude are also available.

When multiple treatment groups are considered, a form of heterogeneity is treatment by sex and/or gender interaction, which measures the magnitudes of differences in outcome across treatments in one sex or gender compared with the other(s).[87] The concept of assigning study treatment by sex and/or gender interaction applies to a study endpoint (such as probability of survival, adverse event rate) involving the comparison between two treatments. It is important to distinguish between qualitative versus quantitative interactions. Qualitative treatment by sex and/or gender interaction for a parameter refers to the situation where one treatment is superior to the other in one sex or gender, but not in the other sex or other gender(s). Quantitative treatment by sex and/or gender interaction refers to the situation where one treatment is superior to the other in both sexes or multiple genders but by different magnitudes (see Figure 1 below). Quantitative interactions can sometimes be explained by an appropriate transformation of the data. For example, a quantitative interaction representing multiplicative device and sex effects may sometimes be removed with a log transformation. Data transformations that remove quantitative interactions can increase statistical efficiency in estimating device effects. In contrast, qualitative interactions cannot be removed by data transformation and are often of fundamental importance clinically in interpreting the benefit-risk trade-off of a device.

[85] See Footnote 7.

[86] National Academies of Sciences, Engineering, and Medicine 2022. Measuring Sex, Gender Identity, and Sexual Orientation. Washington, DC: The National Academies Press. https://doi.org/10.17226/26424.

[87] Altman, DG, Matthews, JN. (1996). Statistics Notes: Interaction 1: heterogeneity of effects. *BMJ*, 313(7055), 486.

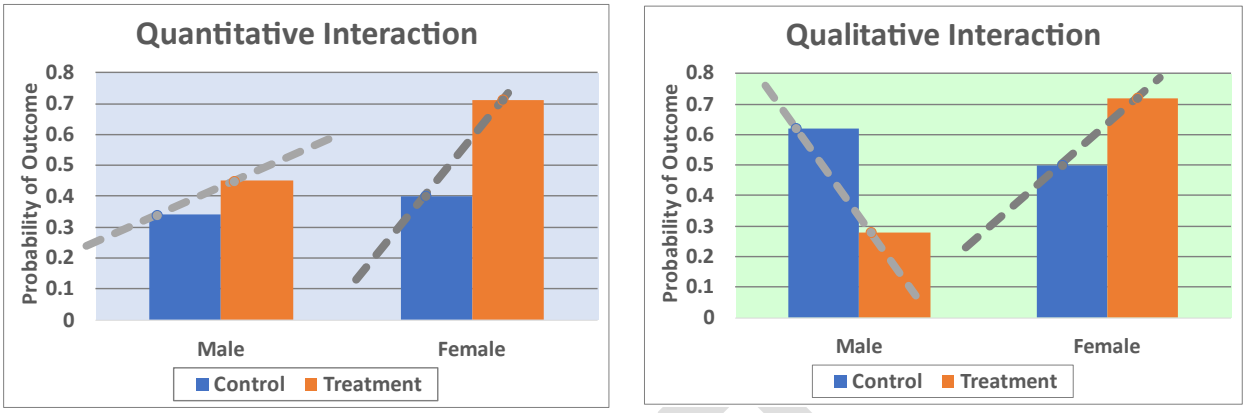


Figure 1. Illustrations of quantitative (left graph) and qualitative (right graph) interactions.

Statistical hypothesis tests of treatment by sex and/or gender interaction have been widely utilized to detect treatment effect heterogeneity across sex and/or gender. Interaction tests have as their null hypothesis the absence of treatment by sex and/or gender interaction. The significance level of an interaction test should be pre-specified in the investigational plan. A test that fails to show statistically significant treatment by sex and/or gender interaction may not be convincing evidence for the absence of clinically relevant interaction as it may lack the power to show such distinction.[88] By the same token, moderate statistical significance may not convincingly demonstrate the presence of clinically relevant interaction. While statistically significant interactions may be investigated for their clinical meaningfulness, clinically relevant interactions that do not reach the threshold of statistical significance may lead to development of further investigation specific to the design and endpoint. In addition to the interaction test, it is recommended to report estimates of differences in treatment effects by sex and/or gender, and corresponding uncertainty around estimated differences.

For studies involving a single treatment with a single device (one-arm study), heterogeneity across sex and/or gender groups can be assessed only for that single treatment and device. The concept of treatment by sex and/or gender interaction has no direct applicability in such studies. To assess heterogeneity, statistical hypothesis tests comparing sex groups or gender groups under the (single) study treatment may be utilized, and in this specific context they are often subject to limitations similar to those besetting the aforementioned statistical tests of treatment by sex and/or gender interaction. In addition, due to lack of treatment comparison by design, the statistical hypothesis tests may be limited in determining whether the difference in outcomes come from treatment effect or prognostic nature of sex and/or gender.

Other study participant characteristics (e.g., weight, body mass index (BMI), co-morbidities, age) correlated with sex and/or gender sometimes might explain apparent sex- and/or gender-specific differences in clinical outcomes. FDA recommends that a sponsor consider adjusting for

[88] Alosh M, Fritsch K, Huque M, Mahjoob K, Pennello G, Rothmann M, Russek-Cohen E, Smith F, Wilson S,Yue L. (2015). Statistical considerations on subgroup analysis in clinical trials. *Statistics in Biopharmaceutical Research*, 7:4, 286-303, DOI: 10.1080/19466315.2015.1077726.

sex- and/or gender-specific differences by incorporating other study participant characteristics and/or treatment-by-factor interaction terms for those factors that may explain observed differences by sex and/or gender.

a. 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 in section VI.C(2) Recommendations for Sex- and/or Gender-Specific Statistical Elements below. In general, to achieve an unbiased estimate of treatment effect in the intended use population, sponsors should provide a strategy to enroll representative proportions of study participants consistent with the sex- and/or gender-specific prevalence of the type of disease or condition that the device is intended to treat or diagnose. Sponsors should make an effort to identify in advance any key covariates that might explain possible differences across sexes and/or genders, plan to collect data on these covariates, and pre-specify a modeling approach to investigate the extent to which these covariates can explain the observed differences.

b. For Completed Studies (premarket submission stage)

In general, all clinical studies should report descriptive statistics for outcomes of interest by sex and/or gender as detailed in Section VI.C(3) below. After overall effectiveness and safety have been investigated, an assessment of the primary endpoints for both safety and effectiveness by study participant characteristics such as sex and/or gender should be considered. If available evidence suggests that there may be clinically meaningful sex- and/or gender-specific differences in outcomes (related to safety and/or effectiveness), results should then be discussed within the premarket submission and considered in the context of available alternative treatments to determine whether additional data collection for males/men, females/women and/or other study participants are needed to address a clinically important question and such data should be included in the premarket submission.

Consideration should also be given, as appropriate, to whether results support premarket authorization of the device in patients of only one sex and/or gender or in patients across multiple sexes and/or genders. In cases where the data supports premarket authorization in only one sex and/or gender, sponsors should consider whether additional data collection might be appropriate. This can include additional premarket data collection in the other sex and/or other genders or postmarket studies aimed at gathering additional information regarding any observed sex- and/or gender-specific differences. If any clinically meaningful sex- and/or gender-specific differences are suspected, either based on pre-specified or exploratory *post hoc* analyses, sponsors should discuss with FDA to determine whether additional data are needed to address any remaining sex- and/or gender-specific questions of safety or effectiveness.

c. For Postmarket Clinical Studies (Post-approval Studies (PAS) or Section 522 Postmarket Surveillance (PS) stage)

For PAS, in some cases FDA may determine that additional study of the device in one sex or other genders is warranted if the premarket study data suggest there are clinically meaningful sex- and/or gender-specific differences.

For PAS involving continuing data collection on IDE cohort study participants, FDA recommends that sponsors conduct the analyses described in Section VI.C(3) below for all follow-up time points.

For PAS (or Section 522 Postmarket Surveillance (PS) studies) involving newly enrolled study participants, sponsors should include the analyses described in Section VI.C(3) below as part of a pre-specified statistical analysis plan in your protocol. Furthermore, if results from sex- and/or gender-specific analyses of premarket data suggest there may be a clinically meaningful difference in outcomes, sponsors should consult with the FDA review team to determine whether this should also be incorporated into the study design and hypothesis for the PAS or Section 522 PS study.

When exploring sex- and/or gender-related differences during analysis of data from a PAS or Section 522 PS study, FDA recommends that sponsors address the issue of confounding by considering study participant characteristics that may confound the relationship between sex, gender, and study outcomes. To evaluate whether other study participant characteristics may explain any differences in treatment effects by sex and/or gender, analyses can include study participant characteristics as covariate and/or treatment-by-factor interaction terms for those factors.

(2) Recommendations for Sex- and/or Gender-Specific Statistical Elements

When Sex and/or Gender Group Differences are Anticipated

- For devices that are appropriate for males/men, females/women and other study participants, where background information or previous clinical study results point to the potential existence of a clinically meaningful difference by sex and/or gender, sponsors may need to intentionally enroll sufficient numbers of study participants in each sex group or gender group(s) (i.e., a sample size sufficient to support meaningful sex- and/or gender-specific claims); stratified endpoint analyses and/or stratified endpoint analyses by sex and/or gender may be warranted. Stratified randomization may also be recommended.
- Where a study plans to include subgroup analyses by sex and gender categories, sponsors should control for Type 1 error rates, as appropriate for the intended use of the device. A common key element of all such study designs is successful control of Type 1 error rates at the desired levels, considering the multiplicity due to the multiple ways to claim study success. Just as with any study having a complex design, the sponsor is encouraged to interact with FDA early in the process through a Pre-submission meeting.[89]
- Although rarely done, it is possible to plan a study that simultaneously investigates the overall treatment effect and the effect on only one subgroup such as females/women (or males/men). This could be done if the intended use were for the entire population or just

[89] For more information on Pre-submission meetings, please see FDA guidance Request for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program.

one pre-identified sex or gender, provided that the study is sufficiently powered for both (i.e., the entire population and the pre-identified subgroup). One approach would be to allocate some fraction *f* of the overall Type I error rate (alpha) to the investigation of the overall inferential procedure and the rest to investigating the particular subgroup. In the hypothesis testing framework, the study would then be successful if either the overall test was significant at level f times alpha or the subgroup were effective at level (1-f) times alpha. For example, the treatment effect (point estimate and its corresponding uncertainty) on the complement sex is recommended to be reported and the sample size in the complement sex should be of sufficient size. The effect should be in the same direction as the specific subgroup when the treatment effect is claimed in the overall population.

- Studies may be designed to investigate overall treatment effect in the combined population, and if positive, conduct additional analyses in one sex and/or gender groups.

Pre-specifying Assessment of Heterogeneity Across Sex and/or Gender Groups in Study Design

- Unless a device to be studied is intended for use in only one sex (e.g., prostate-specific antigen testing for prostate cancer) and/or gender, it is recommended that variability in data across sex and/or gender groups and its interpretation be considered in the study design even if no substantial sex and/or gender difference is expected at the design stage.
- The statistical analysis plan should include a strategy for assessing heterogeneity across sexes or genders as applicable, since FDA recommends such an assessment as an integral part of interpreting study results for every submission. In particular, the heterogeneity assessment can serve as the basis for poolability conditions for studies with prespecified success criteria expressed in terms of data pooled across sex or gender groups. Such poolability conditions bear some resemblance to those commonly used for determining whether data can appropriately be pooled for analysis across different clinical sites. Poolability conditions may be specified as statistical hypothesis tests, which, for studies involving the comparison of two treatments, would typically be tests of treatment by sex and/or gender interaction. The interaction tests should ideally be able to detect interaction of relevant magnitude measured on pertinent parameters with a reasonably high probability, and this goal should guide the choice of appropriate significance level. While statistically significant interactions may be investigated for their clinical meaningfulness, clinically relevant interactions trending towards statistical significance may lead to development of further investigation specific to the design and endpoint.

Additional Considerations for Particular Study Design Types

- For one-arm studies:
  - Sponsors should provide a strategy for assessing heterogeneity across sex and/or gender groups.[90] The specific methodology could vary; if the methodology requires any assumptions, the validity of these assumptions should be investigated.

[90] This type of analysis is currently conducted for the purposes of determining whether data can appropriately be pooled for analysis.

606 - Sponsors may also consider sex- and/or gender-specific objective performance
607 criteria (OPC) or performance goals,[91] which may be used for sex- and/or gender-
608 specific labeling claims. It is important to control overall Type 1 error rate to support
609 multiple labeling claims based on hypothesis testing.
610
611 • For comparative studies:[92]
612 - Sponsors should pre-specify interaction testing. The validity of any assumptions
613 should be investigated.
614 - Sponsors may consider powering for sex- and/or gender-specific labeling claims
615 when sex- and/or gender-subgroup differences are anticipated. If seeking multiple
616 labeling claims based on hypothesis testing, it is important to control overall Type 1
617 error rate.
618 - If the control is non-randomized or historical and study participant-level data exist,
619 then the interaction can be investigated in conjunction with a propensity score data
620 analysis.
621 - For randomized controlled studies, sponsors may consider sex and/or gender as a
622 stratification variable in the randomization process if clinically meaningful sex-
623 and/or gender-specific differences are anticipated.
624
625 Special Considerations for Diagnostic Devices
626
627 For *in vitro* diagnostics, imaging devices, and other diagnostic devices in which a cutoff is used,
628 sponsors should include data from both males/men, females/women, and other study participants
629 both at the cutoff selection and cutoff validation stages. A diagnostic device involves a cutoff
630 whenever a continuous or ordinal measurement is used to separate study participants into two or
631 more categories (e.g., diseased and non-diseased). Separate cutoffs for males/men,
632 females/women, and other study participants should be used only when there is reason to believe
633 separate cutoffs are needed based on previous evidence or if the data in the current clinical study
634 provide evidence for different cutoffs. The use of separate cutoffs may affect study design and
635 sample size calculations.
636
637 Analysis by sex and/or gender of clinical performance measures such as sensitivity, specificity,
638 positive and negative likelihood ratios, and positive and negative predictive values should be
639 performed. Analysis of reference intervals with regard to mean (median) values, standard
640 deviation, and percentiles should be performed for males/men, females/women, and other study
641 participants separately. Separate reference intervals for males/men, females/women and other
642 study participants should be considered only if they will be clinically useful and when there is
643 reason to believe such intervals are needed based on previous evidence. For new measures, if the
644 information necessary to decide these questions is not available, but the data of the reference
645 interval study indicate sex- and/or gender-specific differences, reference intervals should be
646 presented for males/men, females/women and other study participants separately and for

[91] For more information on objective performance criteria (OPC) and performance goals, please see FDA guidance Design Considerations for Pivotal Clinical Investigations for Medical Devices.

[92] For more information on comparative studies, please see FDA guidance Design Considerations for Pivotal Clinical Investigations for Medical Devices.

combined data. Situations may arise in which an assay or device has high overall accuracy (e.g., very high sensitivity and specificity); when this occurs, subgroup analysis may not be warranted.

(3) Recommendations for Analysis of Sex- and/or Gender-Specific Data in Completed Studies

Sex- and/or Gender-Specific Analysis

In general, all studies should report descriptive statistics for outcomes of interest, including the estimate of variance or standard deviation (as applicable) by sex and/or gender. At the primary follow-up time-point, regardless of the potentially limited statistical power of these sex- and/or gender-specific subgroup analyses, data should be examined for clinically meaningful sex- and/or gender-specific differences in each of the following:

- primary effectiveness endpoint(s)
- primary safety endpoint(s)
- secondary endpoints[93]

After overall effectiveness and safety have been investigated, an assessment of the primary endpoints for both safety and effectiveness by study participant characteristics such as sex and/or gender should be considered.

It is important to carry out all analyses set forth in the Statistical Analysis Plan. FDA recommends sponsors plan and conduct analyses to evaluate heterogeneity by sex and/or gender, including treatment by sex and/or gender interaction when applicable, as described in previous sections.

In some cases, the test for treatment by sex and/or gender interaction (or heterogeneity in general) may have adequate power to detect only a very large interaction (or heterogeneity) but may fail to detect a smaller yet clinically important interaction (or heterogeneity). Such situations may arise when the number of study participants in one or all of the sex and/or gender groups is small, in which case additional data from males/men, females/women and/or other study participants may be necessary to support labeling claims. Observed heterogeneity could exist across sexes and/or genders due to large variability associated with small sample sizes; interpretation of clinical meaningfulness may be premature in those cases. Consultation with FDA regarding such analyses and interpretation of data is recommended.[94]

For recommendations on interpreting data, see Section VI.D of this guidance.

[93] Secondary study endpoints can vary in their objective for evaluating device performance and participant experiences with a device. When the secondary endpoint is intended to support a label claim or to define important considerations for treatment decisions, descriptive statistics by sex and/or gender should be reported.

[94] For more information on requesting feedback or meetings for medical device submissions, please see FDA guidance Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program.

Additional Considerations for Data Analysis in Particular Study Design Types

- For one-arm studies:
  - If the overall treatment effect is neither statistically significant nor clinically meaningful, data from subgroup analyses are unlikely to support a premarket submission; however, findings may inform whether a particular subgroup may respond to the treatment that could be prospectively studied.
  - If no significant difference in treatment effect is observed across sexes and/or genders, data may be poolable across sex and/or gender; although such a lack of a significant difference should not be interpreted as evidence of a consistent effect across sexes and/or gender.
  - If a significant difference in treatment effect is observed across sexes and/or genders, it is helpful to perform additional analyses to investigate possible explanations for this difference. Whether data may be poolable across sex and/or gender should be based on the size of the observed treatment difference as well as its clinical importance. Additional data may be necessary to appropriately evaluate the effect of sex and/or gender on the study endpoints. In these cases, discussions with FDA are advised.

- For comparative studies:
  - If overall treatment effect is not statistically significant and clinically meaningful, data from subgroup analyses are unlikely to support a premarket submission; however, findings may inform whether a particular subgroup may respond to the treatment that could be prospectively studied.
  - If no significant interaction effect between treatment and sex and/or gender is observed for the outcome of interest, data may be poolable across sex and/or gender. However, such a lack of a significant interaction effect should not be interpreted as evidence of a consistent effect between treatment and sexes and/or gender. The decision about the validity of pooling the data should be based on the size of the observed treatment difference as well as its clinical importance.
  - If there is evidence of an interaction of treatment by sex and/or gender, it is important to describe the nature of the interaction (qualitative or quantitative) and assess the clinical importance of these differences. Additional analyses may be requested by FDA to investigate possible explanations for these differences, including, but not limited to, adjusting variables and/or interactions between treatment and variables such as age, body mass index (BMI), bone density or concomitant illness (e.g., diabetes). Additional data may also be necessary to appropriately evaluate the effect of sex and/or gender on study endpoints. In these cases, discussions with FDA are advised.
  - If a significant treatment by sex and/or gender interaction has been identified, it may be helpful to explore the effect by assessing whether there is a sex- and/or gender-specific difference in the treatment group only, control group only, or both. Alternatively, the interaction could be explored by assessing whether there is a treatment difference in males or men only, females or women only, or both sexes, or multiple genders.

D. Interpretation of Sex- and/or Gender-Specific Data

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

There are limitations to interpreting clinically meaningful differences in small data sets. Mean differences could exist between sexes and/or genders due to small sample sizes; interpretation about whether they are clinically meaningful may be premature in many cases.

If results of the *post hoc* analysis suggest that there are insufficient data to assess whether sex and/or gender is associated with clinically meaningful differences in outcome, FDA may determine that clinical data from additional study participants in one or both sexes, or one or multiple genders may be needed pre- or post-market to address potential sex- and/or gender-specific questions related to safety and/or effectiveness. In cases where clinically meaningful differences between sexes and/or genders are observed in safety or effectiveness, or when such a difference might be expected but the premarket study did not enroll sufficient numbers from each subgroup to detect it, FDA may request additional studies in one or both sexes, or one or multiple genders to support a premarket submission, implement specific post-approval study conditions, and/or recommend modifications of the design of subsequent studies.

(1) Recommendations for Reporting Sex- and/or Gender-Specific Information in Submissions and Public Documents

Confidential submissions to FDA contain analyses of clinical study data, which may include a variety of sex- and/or gender-specific analyses. However, public documents, which may include, for example, labeling and FDA summaries of review (e.g., Summary of Safety and Effectiveness Data (SSED), Summary of Safety and Probable Benefit (SSPB), SBRA, De Novo Summary) and 510(k) Summaries for medical devices that have been granted premarket authorization, may be inconsistent in the degree of information reported regarding device performance in demographic subgroups. Despite the differences, it is important for generalizability, scientific understanding, and patient and health care professional understanding that both confidential submissions and public documents contain appropriate sex- and gender- specific information.[95]

Reporting data disaggregated by sex and/or gender expands availability of sex- and gender-specific data and helps to inform the benefits and risks of devices for the intended population.

For premarket submissions, FDA recommends researchers analyze and report on data already generated, whether it is sex-based, gender-based, or both as appropriate for the scientific question being studied.[96] However, FDA does not anticipate that researchers will collect both sex and gender data for each clinical study, unless indicated by the scientific question at hand.

[95] For more information on labeling, please see FDA guidances Labeling – Regulatory Requirements for Medical Devices (FDA 89—4203) and Device Labeling Guidance #G91-1 (Blue Book Memo).

[96] For more information on data and terminology standards sponsors may use when submitting to FDA, please see CDRH's website on Data Standards and Terminology Standards for Information Submitted to CDRH.

When reporting on sex- and/or gender-based data, FDA recommends sponsors report any sex- and/or gender-specific limitations of the clinical study in your submission.

(2) Enrollment Demographics, Baseline Characteristics, and Co-Morbidities

Because the enrollment demographics of the clinical study may impact the generalizability of the conclusions, FDA recommends that sponsors report the number and proportion of study participants by sex and/or gender who were treated or diagnosed with the device as part of a clinical study as follows:

- Sponsors should report clinical study demographics in terms of proportion enrolled by subgroup. Reported sex and gender information for clinical studies often reflects gender as a proxy for sex,[97] and in most clinical studies, it is not possible to conduct detailed genetic evaluation to determine the genetic make-up of all study participants. When reporting sex demographics, FDA recommends that sponsors report the method by which sex was ascertained (study participant report, genetic testing, or other means).[98] Sponsors should report gender based on study participant report.
- Sponsors should discuss whether the proportions enrolled are consistent with the sex- and/or gender-specific prevalence of disease, if known. If the proportions are not consistent with the known prevalence, sponsors should discuss why they believe the conclusions of the study are generalizable. For studies with multiple arms, sponsors should report enrollment proportions by each sex and/or gender in each arm.
- If co-morbidities and/or other baseline characteristics are collected, FDA recommends that sponsors include this information within a demographic table of results including other factors stratified by sex and/or gender. This may assist in interpreting any differences in outcomes across sex and/or gender.
- FDA recommends a comparison and discussion of sex- and/or gender-specific differences in follow-up compared to at enrollment, for the overall study sample and for each study arm.

Sponsors may choose to adapt the example language below when describing enrollment in their premarket submissions, or may use other language that incorporates the contents described above.

Example Language (Representative Enrollment):

Female enrollees represented 34% of the total study participants enrolled in the overall study, and 37% of the study participants evaluated for the primary endpoint. This is similar to the proportion of female patients treated for coronary artery disease in the general U.S. population [citation]. Among study participants in the treatment group, 35/100 (35%) were female, and 33/100 (33%) of study participants in the control group were female.

[97] See Footnotes 12 and 35.

[98] Heidari S, Babor TF, De Castro P, Tort S, Curno M. (2016). Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. *Res Integr Peer Rev, 1*(1),1-9.

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

Additionally, FDA recommends that sponsors include this type of information in any applicable tables and charts (e.g., study demographics table, baseline characteristics table).

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

Sponsors should report this information as part of their progress reports (see 21 CFR 812.150(b)(5)) and in the results section of the final study report.

b. For Completed Studies (premarket submission stage)

Sponsors should report this information as part of the premarket submission in sections containing results of clinical studies, including the labeling. A summary of this information should also be included in any draft PMA SSED, HDE SSPB, 510(k) Summary, or De Novo Summary submitted to FDA.

c. For Postmarket Clinical Studies (Post-approval Studies (PAS) or Section 522 Postmarket Surveillance (PS) stage)

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

(3) Sex- and Gender-Specific Outcomes (Safety or Effectiveness)

Sex- and/or gender-specific outcomes analyses should be described in the labeling and summaries of review, regardless of whether the analyses are pre-specified or *post hoc*. Sponsors should specify the statistical methods used to assess for heterogeneity of treatment differences by sex and/or gender. To provide appropriate context, sponsors should describe any prior scientific evidence suggesting that clinically meaningful differences by sex and/or gender are expected and describe any covariates (such as differences in other baseline characteristics) that might influence outcome differences. The primary safety and effectiveness outcomes should be reported by sex and/or gender, when possible, as well as any other important endpoints.

a. For Completed Studies (premarket submission stage)

When presenting results of prespecified sex- and/or gender-specific analyses, FDA recommends the following:

- Clearly state which analyses were conducted.
- Sponsors may include inferential statistics, including p-values and/or confidence intervals. Sponsors should describe any statistical limitations of the analyses.

When presenting results of *post hoc* sex- and/or gender-specific analyses, FDA recommends the following:

- Clearly state that the sex- and/or gender-specific analyses were unplanned.
- Clearly state which analyses were conducted.
- Use descriptive statistics only (mean, standard deviation, etc.) in public documents such as labeling and any review summaries submitted to FDA. Results in confidential

submissions to FDA can include inferential statistics, with a disclaimer that these are from *post hoc* analyses.

If clinically meaningful sex and/or gender differences in safety or effectiveness are observed, or if there are potential differences that might require follow-up studies, data on benefits and risks should be described separately for males/men, females/women and other study participants in labeling and any review summaries submitted to FDA.

b. For Postmarket Clinical Studies (Post-approval Studies (PAS) or Section 522 Postmarket Surveillance (PS) stage)

When presenting results of sex- and/or gender-specific analyses of PAS or Section 522 PS data, the recommendations pertaining to completed studies, as discussed above, also apply.

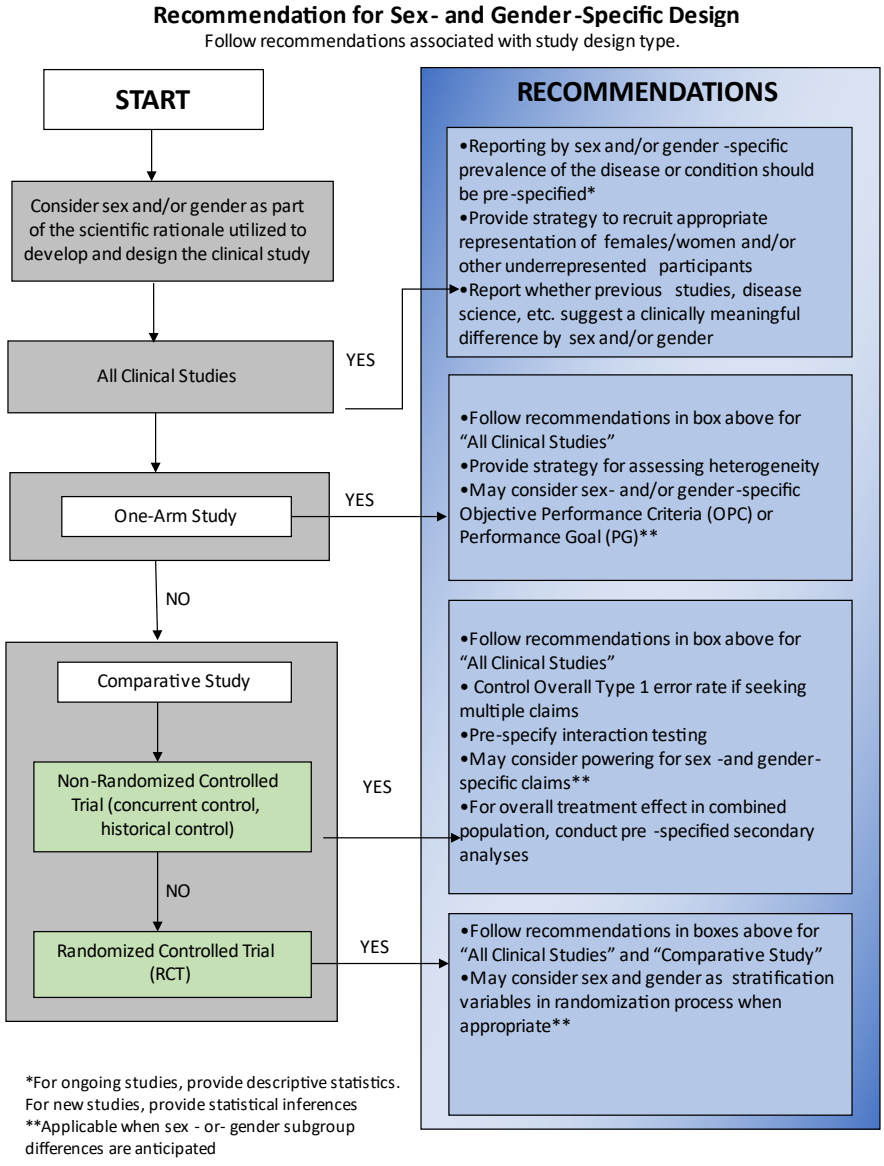
If a clinically meaningful signal is detected in the final analysis, it should be submitted with the final study report. FDA may also request changes to the labeling to reflect the additional safety and/or effectiveness information.

Appendix: Decision Trees

We encourage the use of existing scientific data (e.g., previous studies, disease science) to determine whether there is a hypothesis for a clinically meaningful sex- and/or gender-specific difference for the device. When there may be a clinically-meaningful sex- and/or gender-specific difference for the device, the following decision trees provide a framework in deciding when various sex- and gender-specific statistical recommendations apply for different clinical study designs.

A. Recommendations for Sex- and Gender-Specific Study Design

Follow recommendations associated with study design:

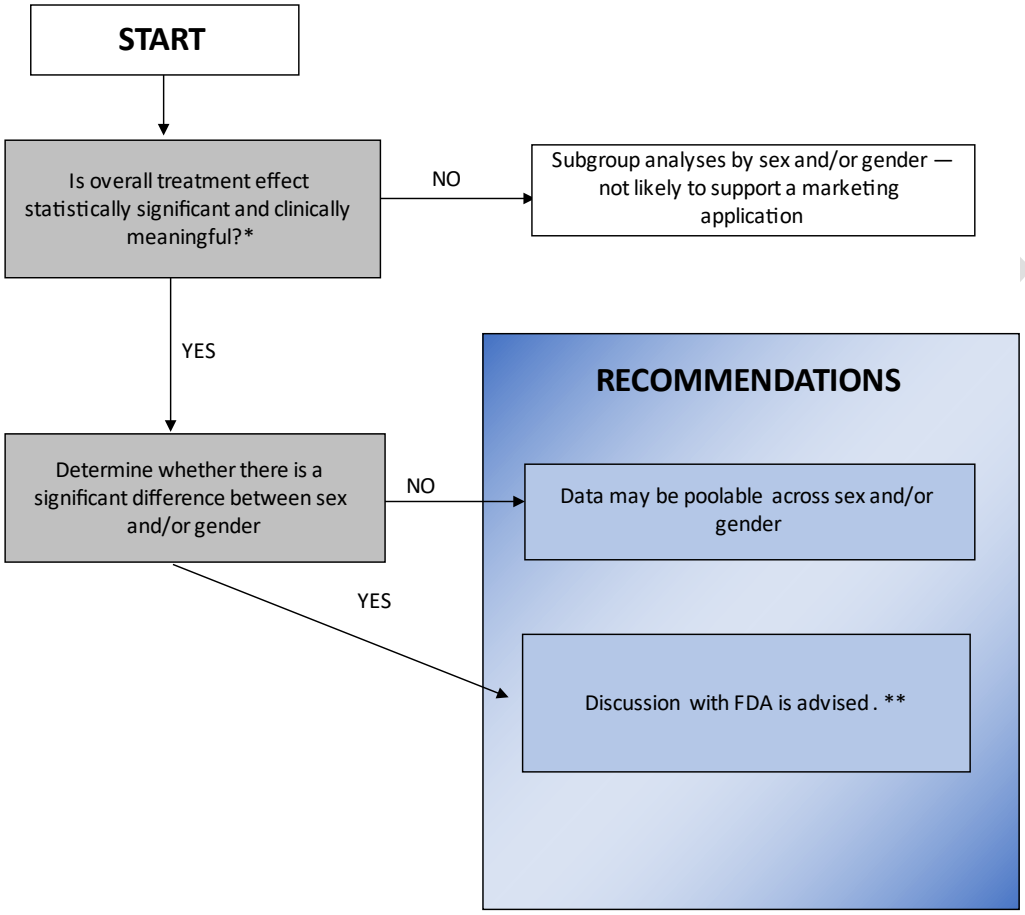


B. Recommendations for Sex- and Gender-Specific Statistical Analysis for Completed Studies – One-Arm Studies

Recommendations for Sex-and Gender - Specific Statistical Analyses for Completed Studies

One-Arm Studies

(Objective Performance Criterion, Performance Goal, Observational Study)



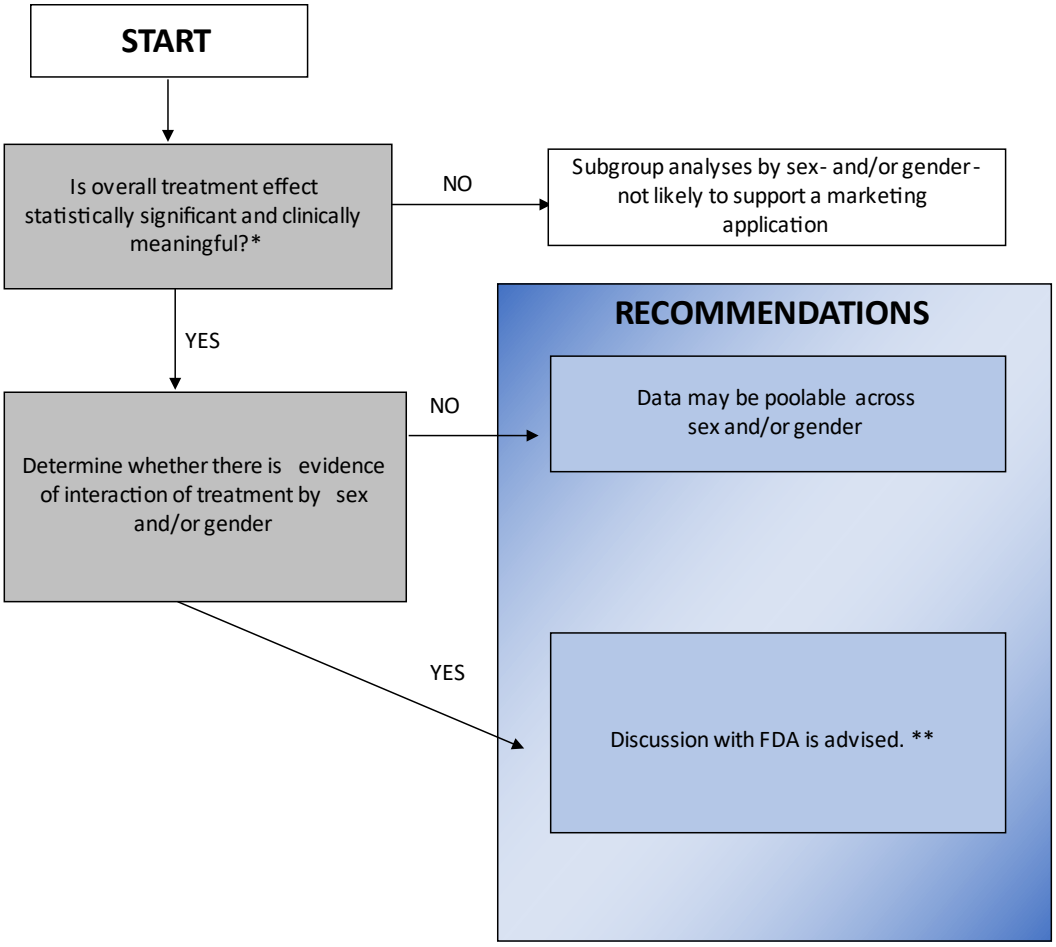
*Subgroup analyses are not recommended if overall treatment effect is not statistically significant and clinically meaningful.

**In some cases, the sex and gender difference could be statistically significant but not clinically meaningful or clinically meaningful but not statistically significant. In these cases, discussion with FDA is advised.

C. Recommendations for Sex- and Gender-Specific Statistical Analysis for Completed Studies – Comparative Studies

Recommendations for Sex-and Gender- Specific Statistical Analyses for Completed Studies

Comparative Studies



*Subgroup analyses are not recommended if overall treatment effect is not statistically significant and clinically meaningful.

** In some cases, the interaction effect could be statistically significant but not clinically meaningful or clinically meaningful but not statistically significant. In these cases, discussion with FDA is advised.