NWX HHS FDA (US)

Moderator: Irene Aihie
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Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode until the question and answer session of today's call. At that time, if you would like to ask a question, you may do so by pressing Star 1. Today's conference is being recorded. If you have any objections, please disconnect at this time. I now would like to turn the meeting over to (Tammy Worth). You may begin.

(Tammy Wirt): Hello and welcome to today's FDA webinar. I'm (Tammy Wirt), the acting branch chief for CDRH Strategic Communication Branch in the Office of Communication and Education.

Today we will be discussing the final guidance document, a valuation of specific data and medical device clinical studies which was released with the FDASIA section 907 action plan on August 20, 2014. The final guidance outlines specific recommendations for considering sex and other variables during the study design stage to improve consistency of analysis and reporting of information on demographics in labeling and other documents.

Today, (Jismi Johnson) from CDRH's Office of Device Evaluation will provide an overview of the guidance including what has changed from draft to final and will answer any questions following the presentation.

Also with us today to assist with the Q&A portion of our webinar, our subject matter experts from the Office of the Center Director and the Office of Surveillance and Biometrics. Following the webinar, the slide presentation, audio recording and written transcripts of today's program will be available on the CDRH learn section of the FDA website. Now I give you (Jismi).

(Jismi Johnson): Good afternoon welcome. My name is (Jismi Johnson) and I'm a reviewer in the Office of Device Evaluation within Center for Devices and Radiological Health. Today we will review the final guidance for industry and FDA staff, evaluation of site specific data and medical device clinical studies which was posted on our website August 20, 2014.

Our presentation today will go over the objectives, scope and background of the guidance followed by a summary of the major comments received on the draft guidance and the major revisions made to the guidance in response. Then we'll provide a brief summary of the guidance content including a decision framework for staff and industry to use. We'll open it up for a question and answer session at the end of the presentation.

This guidance document provides recommendations on the study and evaluation of set specific data and medical device clinical studies. It outlines the Center for Devices and Center for Biologics expectations regarding set specific patient enrollment, data analysis and reporting of device study information. The guidance is intended to improve the quality and consistency of available data regarding the performance of medical devices in both sexes by encouraging appropriate enrollment by sex in device clinical studies and

appropriate interpretation and assessment if the data from such studies are analyzed by sex. We acknowledge that the evaluation of sex specific data in medical device clinical studies benefit patients, their medical providers as well as clinical researchers and others.

The specific objectives of this guidance are to encourage the consideration of sex and associated covariates during the study design stage, to provide recommendations for study design and conduct to encourage appropriate enrollment of each sex, to outline recommended sex specific statistical analyses of study data with the framework for considering sex specific data when interpreting overall study outcomes and finally, to specify FDA's expectations for reporting sex specific information and summaries in labeling for approved or cleared medical devices.

Prior to developing the policy set forth in this guidance, CDRH publicly sought input from a variety of experts and stakeholders regarding the study and evaluation of women in clinical studies for medical devices. This guidance document reflects the recommendation generated in these public workshops and subsequent internal agency discussions. The scope of the guidance clarifies that this document focuses on sex, that the recommendations can be used for enrollment in data analysis by other demographic variables including age, race and ethnicity.

Additionally, we acknowledge that the recommendation for evaluating the impact of the sex demographic variable may not be applicable for all devices. Such cases include certain obstetric gynecological and urologic devices that are intended for single sex or for in vitro diagnostic device clinical studies that you use to identify leftover specimens in which demographic information may not accompany the samples.

We received comments from 17 external stakeholders on the draft guidance. Many comments applied to the statistical section. These included an overall clarification on statistical concepts described as well as comments on when studies should be powered to look for sex difference. When additional data would be needed? Comments on first conducting primary effectiveness analyses and then subgroup analyses and poolability. FDA carefully reviewed all of the comments and modified the draft guidance document to address those.

In response to the comments, the statistics section entitled Considering Sex in Study Design and Data Interpretation was revised to provide more clarity. As we will go into later in the presentation, this section of the guidance was updated to discuss statistical concepts, to set the stage for statistical analyses for sex specific differences, include recommendations for sex specific statistical elements to consider when designing a clinical study, include recommendations for analyzing data from one arm in comparative studies, include recommendations for special considerations to take into account for diagnostic devices and include recommendations for interpreting sex specific data.

This section of the guidance we think addresses the major comments received. It discusses when additional data are needed which was a repeated comment in the docket. If any clinically meaningful sex difference are found, we recommend discussion with FDA on whether additional data are needed to address any remaining sex specific questions.

When clinically meaningful differences between sex are observed in safety or effectiveness, additional data may be required. This section also discusses situations where there's insufficient data to determine if sex is associated with differences.

This guidance document defines sex and gender for the Institute of Medicine 2001 Consensus Report. Sex refers to the classification of things generally as male or female according to their reproductive organs and functions assigned by chromosomal complement. Gender refers to a person's 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. 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.

Certain medical products elicit different responses in women compared to men. Differences may be attributable to intrinsic of extrinsic factors or interactions between these factors. Covariates associated with female sex such as size, age, comorbidity may be responsible for certain differences in safety, effectiveness or design attributes such as failure mode. The final guidance now provides three examples of where sex differences in a device clinical study impacted FDA's regulatory considerations.

In the first example, a clinical study of a next generation ventricular assist device showed that in subjects treated with investigational device, female sex or covariates associated with sex -- such as body surface area -- were found to be correlated with a higher rate of stroke in women as compared to men. There were also trends towards increased rates of bleeding and infection in women compared to men. For this product, 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.

In another example related to cardiac resynchronization therapy defibrillators or CRT-D, the benefit of CRT-D therapy over implantable cardio defibrillator alone was observed to be greater in women than men. Since the sex specific analysis was post hoc, the findings were considered exploratory. In this case, 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.

The metal on metal hip example was added to the final guidance. In June 2012, the orthopedic and rehabilitation devices advisory panel met to discuss the clinical performance of metal on metal hip implants as well as associated adverse events. The total hip replacement and hip resurfacing studies that identified revision rates by sex showed that the revision rate appeared higher among women three to five years post implantation in most studies.

From the panel deliberations, FDA issued a safety communication on metal on metal hip implants including a recommendation for orthopedic surgeons that women may be at risk for increased device wear and/or adverse local tissue reactions and should be followed more closely.

Historically, women have been under represented or excluded from many clinical studies. This has lead to a lack of information available for women and their physicians regarding the risks and benefits of many medical treatments and diagnostic procedures. The lack of available data for women as illustrated by this summary timeline that highlights policy in various reports issued over the years starting with the exclusion of women of childbearing potential from drug studies in the 1970's to an FDA report to congress published in 2013 that showed participation rates for women varied widely by device product area.

The lack of available data is also impacted by barriers to enrollment of women in clinical studies. There are numerous reasons for lower participation rates of women. Some of the key reasons identified by participants at the 2008 workshop include a lack of understanding about the main obstacles to participation of women in clinical research, inclusion/exclusion criteria that may not be necessary and may unintentionally exclude women, a lack of understanding about differences in disease etiology and pathophysiology that may lead to under diagnosis and under referral of women, device manufacturing limitations to accommodate anatomical differences between women and men among other reasons.

It remains important that clinical trials include diverse populations which reflect the intended population whenever possible and appropriate. In general, to achieve an unbiased estimate of treatment effect in the overall population, sponsors should plan to enroll representative proportions of women and men. However, in cases where there be science or prior clinical study results suggest treatment affect in only sex, sponsors may need to intentionally enroll sufficient numbers to support a valid analysis, for example, for sex specific claims.

We recommend that sponsors investigate whether sex differences may or may not exist for the disease or condition which our device is intended to treat or diagnose. The guidance provides approaches to increase enrollment of women in a clinical study. These include, for example, targeting clinical sites where recruitment of women is more easily facilitated, considering revision to the enrollment criteria when appropriate or considering parallel cohorts for collecting data on devices in women and investigating reasons for under enrollment or non enrollment of women. This approach can also be applied to other key demographic groups.

The guidance provides enrollment recommendations for various stages of clinical study design including new or ongoing studies, completed studies and post market studies. The guidance also provides recommendations for sponsors and investigators to help avoid or minimize loss to follow-up regardless of sex.

The next section of the guidance, Section 5, discusses considering sex in study design and data interpretation. We received more comments by stakeholders on this section. As such, to add clarification of the concepts and clearly distinguish the recommendations for the design stage versus analysis of data, this section was revised the most. Unless the investigational device is intended for use in only one sex, it is important that the variation in data across sex be considered in both study design and interpretation of study data.

In this section of the guidance, we introduce statistical concepts for assessing heterogeneity across sex groups. Here, heterogeneity refers to a difference and outcome across sexes. The first subsection identifies and defines statistical terms and tasks related to sex specific statistical analyses to ensure a mutual understanding of the concepts before diving into the recommendations. After introducing the concepts, general recommendations are provided for new or ongoing studies, completed studies and for post marketing studies.

The next sub section provides recommendations to consider for the study design stage. These include recommendations when sex group differences are anticipated, pre specifying assessment of heterogeneity across sex groups in study design, additional considerations for designing one arm and comparative studies and study design considerations for diagnostic devices. As a note to keep in mind, these concepts and recommendations are also captured in the first decision framework on Page 24 of the guidance. The decision framework will be discussed in further detail in a few slides.

The next subsection, called Section 5, describes the recommendations for analysis and interpretation of sex specific data in completed studies. Here we outline recommendations for reporting the analysis of clinically meaningful sex differences.

In general, all studies should report descriptive statistics for outcomes of interest by sex. This analysis should examine data for clinically meaningful sex differences and the primary effectiveness and safety endpoints as well as key secondary endpoints at the primary follow-up time point regardless of the potentially limited statistical power of these sex specific subgroup analyses.

We also delineate additional considerations for data analysis, for one arm studies and comparative studies and finally, Section 5 of the guidance includes a subsection on the interpretation of sex specific data. In this section, we recommend discussing with FDA whether additional data are needed to address any remaining sex specific questions if any clinically meaningful sex differences are found.

If the results of your analysis suggests that there's insufficient data to assess whether sex is associated with differences and outcomes, 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.

Although expected to be rare, in cases where clinically meaningful 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.

We also acknowledge that there are limitations to interpreting clinically meaningful differences in small data sets. As previously mentioned, these recommendations are pictorially represented by the decision framework at the end of the guidance which we will discuss in further detail.

Although sponsors may be the most interested in the generalizability of the findings, individual patients and their medical providers may benefit from more data regarding effectiveness and potential adverse events associated with device use in a particular demographic subgroup. In Section 6 of the guidance, we recommend that you report the number and proportion of subjects by sex who are treated or diagnosed with your device as part of a clinical study. This includes reporting enrollment of demographics, baseline characteristics and comorbidities. The guidance provides example language for sponsors to consider and use when reporting this information in the public documents.

Information regarding sex specific outcomes analyses should be described in the labeling and review summaries regardless of whether the analyses are pre specified or post hoc. Covariates that might explain possible outcome differences between sexes should also be described. If outcome differences by sex are statistically significant and clinically meaningful, then the result of the outcome analyses should be reported.

If the result of these analyses suggest a sex different in an endpoint or event that is clinically meaningful but statistical significance is not reached, sponsors should report the findings descriptively. If the results of these analyses suggest no sex differences in outcomes, sponsors should report which analyses were conducted and that no differences were found.

As mentioned previously, many commenters were concerned that the guidance recommendations applied to each and every clinical study and wanted clarification on when additional data would be needed, when certain recommendations apply and to which studies. Some commenters also recommended a decision framework to provide guidance in these situations. We took that into consideration and AdvaMed provided additional input and suggested content to consider for a decision framework for industry and FDA staff to use.

We work internally with our statistical colleagues to come up with a decision tree for the study design phase as well as decision trees for analyses upon completion of the clinical studies. The decision trees that we will discuss in the next few slides are a pictorial representation of the recommendations described in the tasks of Section 5 of the guidance document which discusses the statistical consideration of study design and analysis.

The first decision tree provides recommendations to consider at the design stage. This framework starts off asking whether the product used is intended for single sex or both sexes. If it is limited to one sex, then no separate sex analyses would be required. If the device will be used in both sexes, you would move down the flow chart to recommendations to consider for all clinical studies.

The recommendations for all clinical studies include pre specifying reporting by sex, providing a strategy to recruit appropriate representation of women which would ideally match the disease prevalence by sex, and reporting other information including previous studies and disease science suggest a clinical meaningful difference by sex. Regardless of the type of study design you use -- single arm or comparative studies -- we believe that these recommendations would apply to all clinical studies. After that recommendation box, the flow

chart breaks down recommendations by type of clinical study: one arm study and comparative study.

For a one arm study, you would follow all of the recommendations proposed previously for all clinical studies and then also provide a strategy for assessing heterogeneity. For a one arm study, you may also consider sex specific objective performance criteria or a performance goal which would be applicable when sex subgroup differences are anticipated.

An objective performance criteria or OPC refers to a numerical target value derived from historical data from clinical studies and/or registries. For example, developed via meta-analytic review of multiple clinical studies on similar devices with sufficiently mature technology. A performance goal, or PG, refers to a numerical value generated by data which may not be as robust as those used to develop an OPC. Generally, the device technology is not as well developed or mature for use of the PG as for an OPC.

Then we move onto the statistical design recommendations for a comparative study. For comparative studies which covers non randomized controlled and randomized controlled clinical trials, you would, again, follow the recommendations for all clinical studies, control the overall type 1 error rate of seeking multiple claims, pre specify interaction testing and consider powering for sex specific claims when sex subgroup differences are anticipated. For randomized controlled clinical trials, you may consider sex as a stratification variable in the randomization process when appropriate and when sex subgroup differences are anticipated.

The next two decision frameworks apply to the analysis stage of completed clinical studies with recommendations for one arm and comparative studies. For one arm studies including OPC, PG and observational studies, the

decision framework starts with the initial question of is the overall treatment affect statistically significant and clinically meaningful? If not, then this would suggest that the analysis raises questions about whether the data can support our marketing application. It is also recommended that subgroup analyses not be conducted if the overall treatment affect is not statistically significant and clinically meaningful.

If the overall treatment effect is statistically significant and clinically meaningful, then you would continue down the flow chart to the next few decision points.

The next decision point asks that you determine whether there's a significant difference between sexes. If there is not then the data may be poolable across sex. If there is a significant difference between sexes, then the next decision points asks, is the sex difference clinically meaningful or statistically significant after adjusting for other covariates? If not, the data may be poolable across sex. If the sex difference is clinically meaningful and statistically significant after adjustment for covariates, then the data may not be poolable cross sex, analyses should be conducted separately and additional data may be required.

We also acknowledge that there will be gray areas for some clinical study results and marketing submissions. Therefore, in these situations where the sex difference could not be statistically significant but not clinically meaningful or clinically meaningful but not statistically significant, discussion with FDA is advised.

Similar to the decision framework for a one arm study, a decision framework was also created for comparative studies. For comparative studies, the framework asks the same initial question of is the overall treatment affect

statistically significant and clinically meaningful? If not, then this would suggest that the analysis raises questions about whether the data can support a marketing application and in this situation, subgroup analyses are not recommended if the overall treatment affect is not statistically significant and clinically meaningful.

If the overall treatment effective is statistically significant and clinically meaningful, then you would continue down the flow chart. The next decision point asks you to determine whether there's a significant interaction effect between sex and the treatment and group for the outcome of interest. If there is not, then the data may be poolable across sex.

If there is a significant interaction affect, the next decision point asks, is the interaction affect clinically meaningful and statistically significant after adjusting for other covariates? If not, the data may be poolable across sex.

If the interaction effect is clinically meaningful and statistically significant after adjustment for covariates, then the data may not be poolable across sex, analyses should be conducted separately and additional data may be required.

For comparative studies, your analyses and submission should also describe the qualitative or quantitative nature of the interaction and clinical significance of any differences. It is also acknowledge that other subgroup analysis may be needed.

Not every clinical study will be black and white in terms of sex specific data. Therefore, we advise you to discuss with FDA in situations where the sex difference could be statistically significant but not clinically meaningful or vice versa. This ends our formal presentation and now we'll take questions.

Coordinator: Thank you. We will now begin the question and answer session of today's conference. If you would like to ask a question, please do so by pressing Star 1, record your first and last name clearly when prompted. Once again, if you would like to ask a question at this time, please press Star 1. Again, if you would like to ask a question at this time, you may do so by pressing Star 1. One moment please for our first question. Our first question comes from (Ronnie). (Ronnie), your line is now open.

(Ronnie): Thank you. I was wondering if the FDA is now requiring sponsors to go back to those studies that are completed and do the statistical analysis based on gender?

(Jismi Johnson): Thank you for the question. For completed studies, we do want you to - we recommend looking and conducting those analyses. The guidance does provide recommendations for the different stages for new studies or ongoing completed studies and studies that are at the post market stage.

Coordinator: Again, if you would like to ask a question, you may do so by pressing Star 1. One moment please. Our next question comes from (Satish Roman). (Satish), your line is open.

(Satish Roman): Hello. Can you hear me?

(Jismi Johnson): Yes.

(Satish Roman): So the guidance has been written for the analysis of overall (unintelligible) affect being statistically significant without consideration for a non (unintelligible) trials. What about non inferiority trials? What analyses are required for such trials?

(Lilly Yue): Good question. Thank you. This is Lilly Yue. I would say that's the same for either a superiority study or a non inferiority study.

(Satish Roman): I'm sorry. I couldn't follow you clearly.

(Lilly Yue) Okay. The requirement is the same for either a superiority study or a non-inferiority study.

(Satish Roman): Okay. Thanks.

Coordinator: Our next question comes from (Susan Campbell). (Susan), your line is now open.

(Susan Campbell): Yes. Thank you. I just wanted to clarify. On the sex specific analysis, I believe you said that reporting must be done regardless of power and so I'm just wondering how a sponsor could say that there were not enough women in the trial and therefore, the analysis can't be done and what is FDA going to do in that case?

(Jismi Johnson): Thank you for the question. Dr. Lilly Yue will be answering that.

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Lilly Yue: That is a good question. Usually, we calculate power, study power, based on, for example, the treatment difference for primary effectiveness or safety endpoint. We may not have sufficient power for testing sex difference. But, no matter what, we do need to report study results by sex.

(Jismi Johnson): For future questions, if everyone could identify their affiliation when announcing their name, we would appreciate that. Thank you.

Coordinator: As a reminder, if you would like to ask a question at this time, please press Star 1, record your first and last name along with your affiliation. There appears to be no further questions in queue at this time.

(Tammy Wirt): Okay. Thank you. This is (Tammy Wirt). Thank you for your questions today. If you have additional questions, please submit them to dice@fda.hhs.gov. Please remember that this presentation - I'm sorry. Two more questions just came in.

Coordinator: One moment please. Our next question comes from (Jessica). I'm sorry (Jessica). I'm going to have you to announce your affiliation. It was a little difficult to make out but (Jessica), your line is now open.

(Jessica): Yes. (Jessica) with (Roche) and our question is regarding transgender. We've had studies where people have identified themselves as transgender and are taking hormones to either be more male and/or more female like. How should the sponsor handle that when we run into situations like that?

(Jismi Johnson): Thank you for your comment and question. We did get this comment also to the docket and we understand that there will be unique considerations for this group and we do have different forums that are looking into this. For example, the health and women program but I think this would need to be handled on a case by case basis during the pre submission phase or the early study design stage. Does that answer your question?

(Jessica): No. I mean, because we're not going to know that in the early design stage. You would find that out when you're recruiting your subjects and all of a sudden you have one that tells you, by the way, I'm born male but now I'm female.

(Jismi Johnson): I don't have a good answer for you for this specific situation. I think when we get those situations, there will be a little bit more discussion just because at this moment, we haven't had that specific situation I think. We will continue to discuss and hopefully have an answer when that situation actually does arise.

(Jessica): Thank you.

(Jismi Johnson): Sure.

Coordinator: Our next question comes from (Beta) with Pita Medical. (Beta), your line is now open.

(Beta): Thank you. I'm just actually calling to find out if this adversely affects the 510K submission? We've already submitted our 510K application and I want to know whether or not we'd have to do any further follow-up on old studies that we use to supplement this application for sex specific data.

(Jismi Johnson): I think for that specific submission you should contact FDA and there will be discussion between the review division, the statistics folks on your specific situation.

(Beta): Okay.

(Jismi Johnson): Thank you.

Coordinator: Our next question comes from (Tonya Desenza) with (unintelligible). Your line is now open (Tonya).

(Tonya): Yes. Hello. We asked a question in the chat. It was just a technical question to know the name of the presenter. We hadn't caught that. I'm sorry.

(Jismi Johnson): (Jismi Johnson), Biomedical Engineer in Office of Device Evaluation.

(Tonya): (Jismi Johnson)?

(Jismi Johnson): (Jismi) yes. J-I-S-M-I, last name (Johnson).

(Tonya): Thank you very much.

Coordinator: As a reminder, if you would like to ask a question, please press Star 1, record your first and last name clearly along with your affiliation when prompted.

(Tammy Worth): Okay. If there are no more questions, again, thank you for attending today's webinar and for your questions. If you have additional questions, again, you can submit them to dice@fda.hhs.gov and someone will get back to you promptly. This presentation will be available on the CDHR learn section of fda.gov. The written transcript and recording may take a couple of days to be posted but should be posted no later than Friday, August 29. If you have further questions, you can also use the contact information provided at the end of this slide. As always, we appreciate your feedback on today's presentation, thank you for participating and this concludes today's webinar.

Coordinator: Once again, this now concludes today's conference. All lines may disconnect at this time.

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