To: Food and Drug Administration, HHS

Re: Docket No. FDA- 2024-D-4245

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to respond to the FDA request for comment regarding the draft guidance document: *Study of Sex Differences in the Clinical Evaluation of Medical Products.*

The ISCTM offers these comments for consideration based on our experience and expertise in human CNS research. The ISCTM is an independent organization focused on advancing the development of improved treatments for CNS disorders. No member of this Working Group, comprised of scientists, clinicians, trialists, statisticians and drug developers from both industry and academia, received compensation for comments provided. Comments represent individual opinions and not that of the institution, agency, or company affiliation of group members.

The ISCTM formed a group, led by Abhishek Pratap and Siân Ratcliffe Smethurst, to review and provide comments on behalf of the Society. The authors of the comments provided below are (in alphabetical order):

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General comments

The ISCTM welcomes FDA's draft guidance highlighting importance assessing sex differences in clinical studies. We recognize the importance of these recommendations for developing robust and generalizable medical products.

Finalizing these guidelines is essential for enhancing diversity (including sex) in clinical trials, ensuring reliable data, and complying with the FDORA in the Consolidated Appropriations Act, 2023.

Without representative participation, clinical research cannot fully account for the variability in treatment responses across different populations, leading to gaps in care and ineffective treatments for certain groups (National Academies of Sciences, Engineering, and Medicine et al., 2022). Ensuring adequate representation in clinical trials that reflects the underlying real-world target patient population is a necessity for creating reliable and generalizable data (National Academies of Sciences, Engineering, and Medicine et al., 2022). Recognizing current barriers and designing trials that reflect target patient demographics is crucial for achieving equitable health outcomes (Corneli et al., 2023) and reducing healthcare costs.

Specific comments

Proposed recommendations for deletion marked as strikethrough

Proposed recommendations for addition marked as **bold** text

I. INTRODUCTION

II. BACKGROUND

A. Terminology

Lines 53-54 state *categorized as female or male, but variations occur. Variations of sex refers to differences in sex development or intersex traits.*

ISCTM response: It would be helpful to include in the final guidance how and what data should be captured in such instances (i.e., when sex and gender are not conformant, and/or some biological attributes are more similar to the other sex). Acknowledging the definition of "sex" as being defined at birth, we note that researchers and sponsors working with gender fluid/transitioning individuals may face challenges in the collection and interpretation of data based on this definition. For example, should a transgender male who has transitioned and been on hormonal therapy for ≥ 6 months be documented as male?

B. Data Standards

Lines 89-90 state "*FDA recommends that participants (not the team conducting the trial) self-report sex information, which is generally based on their sex assigned at birth*."

ISCTM response: It would be helpful for FDA add language regarding categorization of intersex individuals in the final guidance or address the issue in a separate guidance.

For certain endocrinological, reproductive, or genetic disorders, self-reported sex may not be sufficient to explain biological differences in drug response. Although FDA states that discussion of inclusion of intersex individuals is beyond the scope of the current draft guidance (lines 74-75), it would be helpful to have additional information on how to handle intersex categorization in regulatory submissions.

Lines 90-92 state *"However, if a participant is unable to self-report their sex (e.g., because of the participant's inability to respond), other sources can be used by the team conducting the trial to collect this information."*

ISCTM response: This phrasing comes across as almost intrusive, as well as dismissive of some participants' concerns around privacy and discrimination. Particularly for stigmatized populations, there is fear of privacy breaches leading to discrimination and personal harm. This may also potentially discourage some vulnerable participants from participating in clinical studies.

Provide additional guidance on what "other sources" might be. Note that these should be based on "appropriate" sources, i.e., not violating subject consent or privacy.

Additionally, the guidance lacks direction on what should be done if the subject declines to self-report. For example, if a transgender person does not wish to disclose their sex assigned at birth because it may reveal their transgender status. In CDISC data standard, is there an option for declining to respond?

ISCTM Recommends rephrasing as follows: *"However, if a participant is unable to self-report their sex (e.g., because of the participant's inability or discomfort in responding), other sources can be used by the team conducting the trial to* ***ethically collect this information while prioritizing patient privacy and preferences, such as birth records, confirmation by a reliable witness, etc., if the participant has consented to accessing such other source information."***

Lines 94-96 *state "Unlike the sex variable, gender is currently not a required data variable for submissions subject to 745A(a) of the FD&C Act14 and is not currently a standardized data field in CDISC. FDA encourages inclusion of gender data particularly if gender may influence the outcome of interest."*

ISCTM Response: We encourage FDA to update this statement and reference the correct CDISC field, or remove it from the final guidance (i.e., "Unlike the sex variable, gender is currently not a required data variable for submissions subject to 745A(a) of the FD&C Act ~~and is not currently a standardized data field in CDISC~~.")

CDISC has published sexual orientation and gender (SOGI) standards that should be referenced here https://www.cdisc.org/kb/ecrf/sexual-orientatio-gender-identity-sogi

C. Representation of Female Participants in Clinical Trials and Non-Interventional Studies

No comment

D. Why Consider Sex Differences in Medical Product Development?

No comment

III. CLINICAL TRIAL DESIGN AND CONDUCT

A. Recruitment, Enrollment, and Retention

Lines 197-227

ISCTM Response: Recommend adding the proposed bullet to this list of strategies to increase recruitment, enrollment, and retention: **Consider differential compensation with clear explanation of the rationale to enable greater participation of women, given gendered wealth disparities.**

Lines 209-214 state *"Consider the use of mobile medical professionals, such as nurses and phlebotomists, to visit participants at their locations instead of requiring participants to visit clinical trial sites. Consider using a digital health technology to collect information directly from participants at their locations rather than having to travel to trial sites."*

ISCTM Response: Increasing the use of decentralized elements and digital health technologies will be important for making clinical trials more viable for female participants. Use of additional decentralized elements and technology can further mitigate barriers to recruitment and retention.

We suggest that FDA add some additional details to the outlined recommended practices, eg: "Consider the use of mobile medical professionals, such as nurses and phlebotomists, to visit participants at their locations, **as well as direct shipping of investigational products,** instead of requiring participants to visit clinical trial sites." Consider using a digital health technology, **such as wearables or electronic patient reported outcomes,** to collect information directly from participants at their locations rather than having to travel to trial sites."

Line 215

ISCTM response: Differences in medication adherence between men and women. In hypercholesterolemia, women exhibited poorer adherence to statin therapy compared to men, with statin-related side effects and patient perception being significant factors. Adherence to anti-hypertensive therapy showed conflicting results, with studies reporting both higher and lower adherence in women. (Vendetti et al, 2023)

Consider adding text regarding differences in medication adherence between men and women, with suggestion to add **Where appropriate or applicable, sponsors may consider implementing baseline and ongoing assessments of medication adherence using validated tools to identify participants at risk of nonadherence due to sex differences in adherence to medication regimens.**

Lines 218-219 state *"Enroll females of different ages, races, ethnicities, hormonal statuses (e.g., menopausal), and comorbidities, as applicable"*

ISCTM response: To ensure a more representative cross section of the female population, there are additional categories that should be considered for inclusion in clinical trials.

We suggest that FDA adding to this non-exhaustive list of categories: "Enroll females of different ages, races, ethnicities, hormonal statuses **(e.g., pre-, peri-, and post-menopausal, pregnant, lactating), gender identities, sexual orientations, geographic locations,** and comorbidities, as applicable."

As study retention can vary across diverse populations, we recommend adding language for sponsors to consider study design aspects to address retention.

Proposed example text to add: **"Include in study design considerations for retaining subjects of ages, races, and ethnicities that are of known higher risk for attrition."**

B. Trial Design

No comment

C. Enrollment of Participants Who Are Pregnant and/or Lactating

No comment

IV. STATISTICAL CONCEPTS

A. Overview

Lines 290-297

ISCTM response: Adherence to medication can influence drug efficacy and overall health outcomes (Brown & Bussell, 2011) (Le Flohic et al, 2024).

Consider adding a 5th point ie **(5) assessing whether nonadherence among a specific sex influences drug efficacy and overall treatment outcomes.**

B. Analyses for Differences in Treatment Effects Between Females and Males

Lines 331-334

ISCTM response: The draft guidance states that most statistical tests for detecting sex-based differences in treatment effects are underpowered but does not provide a positive example of how to mitigate or overcome this shortcoming.

It would be helpful for FDA to provide guidance on power considerations and reporting requirements in this paragraph, an/or to provide an example of how sex differences were analyzed in a previous clinical trial.

Lines 337-338 state *"There may be insufficient power for some smaller, but still clinically important, differences in treatment effects by sex."*

ISCTM response: Nonadherence reduces the statistical power of clinical trials. If patients do not adhere to their treatments, variability in treatment responses increases. This masks drug efficacy and may reduce the ability to detect true differences in drug efficacy between sexes (Alsumidaie, 2017).

Consider adding text to acknowledge this:

"There may be insufficient power for some smaller, but still clinically important, differences in treatment effects by sex. **Non uniform adherence can further reduce statistical power by increasing variability in treatment response, making it even more difficult to detect true differences in treatment efficacy between sexes. When adherence is inconsistent, the observed treatment effect may be masked, leading to wider confidence intervals and an increased likelihood of failing to detect clinically meaningful differences in treatment effects by sex."**

Line 345 states “tends to be larger the more similar the subgroup sizes of females and males. Notably, trials and”

ISCTM response: Section IV indicates that it is preferable to calculate the treatment effect for males and females by including an interaction term for sex*treatment in the overall model rather than generating separate subgroup analyses (i.e. analyzing males and females separately). However, throughout section IV the word "subgroup" is used in 2 distinct ways: 1 - in the context of subgroup analyses (where the subgroups are analyzed separately which is not recommended) and 2) using the word "subgroup" in a more general way to refer to the subgroups of participants even when they are included in the same model (which is recommended and includes sex*treatment interaction term). This may cause confusion which may result in sponsors incorrectly performing separate analyses for males and females.

ISCTM recommends updating to “tends to be larger the more similar the **number** ~~subgroup sizes~~ of females and males. Notably, trials and..";

Lines 348-350 state “characteristics. The risk of incorrectly concluding that a treatment-by-factor interaction exists increases as the number of factors increases if such tests are performed without adjusting significance levels for the multiple tests.”

ISCTM response: Consider adding the following wording at the end of the paragraph to emphasize the importance of not sacrificing one axis of diversity for another, as they intersect.

“This does not absolve clinical trialists from recruiting, enrolling, and retaining diverse populations on these other axes. If other factors tend to be underrepresented in clinical trials or non-interventional studies in this disease, consider enrichment of those factors in participants.”

C. Analyses to Estimate Treatment Effects in Females and Males

Line 361 states ”specific treatment effects have greater precision than estimators based solely on the data for a”

ISCTM response: Same rationale as noted for line 345.

ISCTM recommends updating line 361 to "...specific treatment effects **(i.e. including treatment-by-sex interaction in the model)** have greater precision than estimators based solely on the data for a..";

D. Reporting Results of Analyses

Line 381 states *“overall population, the results for each subgroup by sex should be examined to understand”*

ISCTM response: Same rationale as noted for line 345.

ISCTM recommends updating the text to "...overall population, the results for each ~~subgroup by~~ sex should be examined to understand..."

E. Considerations if Differences in Treatment Effects Between Females and Males Are Anticipated at the Design Stage

No comment

V. NONCLINICAL CONSIDERATIONS

No comment

VI. OTHER GENERAL CONSIDERATIONS

Line 455 states “When clinically significant differences in safety or effectiveness between females and”

ISCTM response: The annual adjusted disease-specific economic cost of nonadherence per person can reach $44,190 and cause 125,000 preventable deaths annually. Hence, monitoring adherence post-market is critical to reduce economic costs and save patient lives (Cutler et al, 2018) (Kleinsinger, 2018).

ISCTM recommends to consider adding wording to acknowledge this, ie. “When clinically significant differences in safety, effectiveness, **and/or adherence** between females and…”

REFERENCES

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