6 August 2019

To: Food and Drug Administration, HHS

Re: Docket No. 2019-11978

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to respond to the FDA request for comment regarding the guidance document: *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry*

ISCTM offers these comments for consideration based on our experience and expertise in human CNS research. 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 personal opinions and not that of the institution, agency, or company affiliation of group members.

ISCTM formed a group, led by Atul R. Mahableshwarkar and Debra M. Hoffmeyer to review and provide comments on behalf of the Society. The authors (in alphabetical order) of the comments provided below are:

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COMMENTS ON ENHANCING THE DIVERSITY OF CLINICAL TRIAL POPULATIONS: ELIGIBILITY CRITERIA, ENROLLMENT PRACTICES, AND TRIAL DESIGNS GUIDANCE FOR INDUSTRY:

GENERAL COMMENTS

ISCTM welcomes this guidance and is encouraged that the FDA has provided recommendations to sponsors to enhance the diversity of clinical trial populations**.**

ISCTM understands that the FDA is issuing this guidance to satisfy the mandate under section 610(a)(3) of the FDA Reauthorization Act of 2017 (FDARA) (21 U.S.C. 360bbb note), specifically, broadening eligibility criteria to increase diversity in enrollment; considering other study designs for improving enrollment; and broadening eligibility for clinical investigations to treat rare diseases or conditions. Enhancing the diversity of participants who enroll in clinical trials will increase our understanding of the risk/benefit profile of drugs and potentially increase the generalizability of the efficacy results. However, there remain cautions, questions surrounding participant payments, safety assurances, and complexities surrounding pediatric programs, etc., which should be considered when seeking to study a wider population than may be currently enrolled in development programs. There remains risks and limitations related to the utilization as noted in the guidance, (Lines 158, 179, 227 and, 317). There are also concerns regarding the unilateral application of such guidance to accomplish diversity in registration trials, complicating these trials, when additional studies can be employed to obtain data in broader patient populations, often with greater efficiency and appropriate sequencing to address safety concerns. Additional considerations surround the guidance possibly increasing standard variations and placebo response. Lastly, there are concerns regarding how such a diversity of participants may be appropriately reflected in safety labeling and may ultimately make drawing clear conclusions difficult.

ISCTM looks forward to the adoption of guidance that clearly advances the methodology intended to enhance the diversity of clinical trial populations, eligibility criteria, enrollment practices and trial designs. ISCTM is prepared to and would readily participate in further public debate to achieve this goal.

II. BROADENING ELIGIBILITY CRITERIA TO INCREASE DIVERSITY IN ENROLLMENT

Lines 48-50 offer FDA guidance examples of participants: *"excluding participants for whom the risk of an adverse event is not likely to be reasonable in relation to any potential benefit and the importance of the knowledge that may be expected to result."* ISCTM agrees with the guidance

examples and, since the liver is the major organ for metabolism, hepatic function may be a major reason for exclusion of patients, ISCTM requests the following language change from, *"example, patients with decreased renal function or certain concomitant illnesses are often excluded because of concerns that they may be more susceptible to the adverse effects of an investigational drug because it is metabolized by the kidney or interacts with other medications."* to the following text, "example, patients with decreased hepatic, renal function or certain concomitant illnesses are often excluded because of concerns that they may be more susceptible to the adverse effects of an investigational drug because it is metabolized by the liver, kidney or interacts with other medications."

Lines 63- 64 state *"...often excluded from trials without strong clinical or scientific justification."* ISCTM suggests that the term "strong" is ambiguous and does not address the frequent absence of clear rationale for the exclusion and proposes the FDA consider using the language, "without clear and strong" on Line 63. Additionally, ISCTM requests including population example after *"HIV"* prior to *"children", "*individuals with suicidal ideations and behavior", as individuals with prior history of suicidal ideation and behavior are often excluded from trials without adequate rationale.

ISCTM agrees with line 66-68. However, we encourage the FDA to consider updating line 66 to state, "participants with complex health issues with appropriate safeguards" in place of *"complex participants".* ISCTM suggests adding "appropriate safeguards" as a particularly important guidance on broadening eligibility to increase diversity in enrollment and such wording may be appropriate at other places in the guidance.

II.A. Broadening Eligibility Criteria in Enriched Clinical Trials

The document states in line 89- 91 that *"FDA encourages the use of enrichment strategies to increase the potential of a trial to detect an effect of the investigational drug, although it is often advisable to include a reasonable sample of participants who have the disease but do not meet the prognostic or predictive enrichment characteristics prespecified in the clinical trial*." ISCTM agrees with this guidance; however, ISCTM suggests adding "This may often be accomplished by enrollment of a broader population into the trial with the primary analysis population narrowed (e.g. as described at line 167)." ISCTM submits that the existing language implies that patients who do not meet specified eligibility criteria may be enrolled and this may give a competitive advantage to the duplicate and professional subject, who can change their presentation between sites, over bona fide patients who present with "real" symptoms and conditions. Additionally, including a cohort of participants who do not meet the enrichment criteria could increase the sample size needed for the trial and would increase time to enroll participants and increase costs for the development programs.

II.B. FDA Recommendations

II.B.1. Inclusive Trial Practices

ISCTM agrees that several different methodological approaches and trial design considerations may be utilized to increase the enrollment of a broader patient population. Such approaches should consider impact on signal detection including the possibility of increasing participant expectations of benefit thus potentially increasing placebo response and the possibility of enrolling *duplicate and professional participants, who may be enrolling in clinical trials for motives other than to advance science or may indeed not even have the condition being studied.*

The second sentence line 106 -108 is not clear and is redundant. ISCTM recommends the line to simply state, "If not needed to assure trial participants safety, consider eliminating."

ISCTM recommends FDA add the following words to line 132-133 to clarify that this thinking comes from guidance issued for oncology trials. *"Consider including children (ages 2 to 11 years) and adolescents (ages 12 to 17 years) in confirmatory clinical trials involving adults when appropriate* as has been stated in guidance issued for oncology trials and more thoroughly discussed in lines 158-165."

II.B.2. Trial Design and Methodological Approaches

ISCTM agrees with line 144, *"Alternatively, an expansion cohort…"* may be used to assess specific populations. However, we suggest including "an expansion cohort or other adaptive designs."

Line 167-176: ISCTM suggests changing lines from, *"Consider including a broader participant group in the trial as part of the secondary efficacy and safety analyses, even when the primary analysis population is narrowed (e.g., when using enrichment designs)"* to, "Consider including an adequate number of participants across a wider range of disease severity in the trial as part of the secondary efficacy and safety analyses, even when the primary analysis population is narrowed to only a particular stage or severity of the disease (e.g., when using enrichment designs)." To make this approach useful there should be enough people in that additional cohort to obtain adequately informative understanding of the efficacy and/or safety of the drug in those patients. This approach allows the study to utilize enrichment to help demonstrate effectiveness while also providing information on effectiveness and safety in a broader population and not decreasing the chances of achieving success on the primary clinical endpoint.

ISCTM agrees with the FDA lines 178-185, that important information regarding drug metabolism during pregnancy and across trimesters, a time when physiology changes significantly, is not obtained during drug development. Collecting pharmacokinetic samples may provide some such knowledge. However, the process of establishing the safety of a drug for women during pregnancy and of the unborn child is not well established. Questions such as, A) Are toxicological data as they are currently collected considered sufficient to permit exposure of women who get pregnant during a trial and would be in the first trimester of pregnancy with ongoing organogenesis? B) What level of evidence is required to establish if it is safe enough to continue Investigational Medicinal Products (IMP) in a pregnant woman? Safety for both mother and child need to be considered. C) It is uncertain if any meaningful conclusion can be drawn based on the PK parameters collected during a pregnancy from a single/few trial participant, etc. Given the examples of some concerns that are raised when suggesting continued participation of pregnant women in trials with drugs where the benefit/risk profile has not been established, ISCTM suggests that approach to broadening participation in trials be carefully thought out and any implementation should have a broad agreement of the field and suggests the FDA develop further guidance in the future to address these and other questions.

Lines178-185. ISCTM proposes important information regarding treatment response, safety and drug metabolism during pregnancy and across trimesters, a time when physiology changes significantly, are not obtained during drug development. Continued participation of women who become pregnant while enrolled in trials and collecting pharmacokinetic samples would provide

such knowledge. However, in allowing such participation, ISCTM recommends FDA should very carefully consider the safety of both the mother and the unborn child, and in the presence of any uncertainty assume a well-considered and conservative approach.

III. OTHER STUDY DESIGN AND CONDUCT CONSIDERATIONS FOR IMPROVING ENROLLMENT

III.A. Make Trial Participation Less Burdensome for Participants

Ecological Momentary Assessments (EMA) provide important data for clinical trials and are capable of recording and transmitting information collected from study participants at multiple time points and geographically distant from clinical trial sites. Therefore, ISCTM recommends including EMA, geolocation and other smartphone capacities in the definition of mobile technology. Page 7, definition, citation 18.

ISCTM agrees with the FDA that in addition to stringent eligibility criteria, potential participants face many additional challenges to participating in burdensome clinical trials including overly complex informed consent forms. While reimbursement for expenses incurred and modest payments for time needed for study activities is not unreasonable, the suggestion of paying subjects for their participation raises concerns of undue influence, possible coercion and may lead to increases in the number of duplicate and professional participants enrolled in studies. ISCTM proposes adding in lines 220-230–specifically line 226, "particularly in cases, when other recruitment methods are not feasible or have been exhausted".

FDA statement, "*however, FDA recognizes that payment for participation may raise difficult questions."* We suggest changing the text to, "however, FDA recognizes that payment for participation raises many difficult questions."

ISCTM proposes adding a bullet after line 230: "Informed Consent Forms (ICF) have increased in size and complexity. Overly long documents have the potential to obscure important information and reduce willingness of potential participants to enroll in studies. Simplifying ICFs for ease of understanding should be considered when they are written. Consideration may be given to using technological approaches that simplify the process of obtaining informed consent with the understanding that documenting consent would need to follow established procedures."

III.B. Adopt Enrollment and Retention Practices That Enhance Inclusiveness

ISCTM supports the Community-Based Participatory Research Program (CBPR) to aid in scientific researcher and community collaborating to address diseases and condition disproportionately affecting populations. However, we would like to encourage the FDA to clarify that this specifically speaks to the CBPR program and may not effectively meet the needs of potential participants who are not part of that specific population.

We propose FDA start line 239 with "Clinical research designers should be mindful of potential placebo response effects associated with shaping patients' expectations regarding their participation in clinical trials."

ISCTM suggests replacing line 241, *"Understanding how participants choose…*" with the following text: "Understanding why participants choose…".

ISCTM suggests replacing line 245, *"Ensure that clinical trial sites include geographic locations with a higher concentration of racial and ethnic minority patients to recruit a more diverse study population."* with the following text: "consideration should be given to inclusion of clinical trial sites at geographic locations with a higher concentration of racial and ethnic minority patients to recruit a more diverse study population."

ISCTM proposes replacing line 260-262: *"Explore agreements to foster the exchange of medical records between clinical trial sites in order to promote participant retention by obtaining participant consent for clinical trial investigators to transfer medical records, including electronic medical records, when participants move from one location to another, because participants often struggle to navigate the gathering and transfer of records between sites."* with the following text "Explore agreements to foster the exchange of medical records between clinical trial sites in order to promote participant retention. Clinical trial investigators may consider obtaining participant's informed consent to transfer medical records,…"

III.C. Expanded Access

The FDA document states in lines 270-274 that, *"FDA's expanded access regulations provide a pathway to potentially offer such patients, when they have a serious or immediately life-threatening disease or condition, treatment with an investigational drug, provided certain criteria are met, including that there is no comparable or satisfactory alternative therapy."* ISCTM requests FDA consider for clarification the following language; "FDA's expanded access regulations provide a pathway to potentially offer such patients treatment with an investigational drug. Certain criteria must be met, including that they have a serious or immediately life-threatening disease or condition and there is no comparable or satisfactory alternative therapy."

IV. BROADENING ELIGIBILITY CRITERIA AND ENCOURAGING RECRUITMENT FOR CLINICAL TRIALS OF INVESTIGATIONAL DRUGS INTENDED TO TREAT RARE DISEASES OR CONDITIONS

ISCTM agrees with engaging in development process advocacy groups, as suggested in the guidance document (lines 304 -308). We encourage the FDA to consider and note within the guidance document that contacts with patient advocacy groups have the potential to add to placebo response by increasing the effects of subject expectations.
Therefore, ISCTM suggests adding a comment, "In your contacts with such patient advocacy groups be mindful of potential placebo response-increasing effects of shaping inappropriate expectations."

ISCTM agrees with an open-label extension study noted in lines 322-324, "*Make available an open-label extension study after early-phase studies to encourage participation by ensuring that all study participants, including those who received placebo, will ultimately have access to the investigational treatment."* Although ISCTM agrees with the idea, we are concerned that it is not always appropriate, and the guidance should clearly acknowledge this. ISCTM requests the FDA add: "if appropriate and justified based on clear clinical and safety data."