To: Food and Drug Administration, HHS

Re: Docket No. FDA- 2021-D-0789

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to respond to the FDA request for comment*: Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies Guidance for Industry*

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 personal opinions and not that of the institution, agency, or company affiliation of group members.

ISCTM is deeply committed to enhancing clinical trial diversity and has a standing working group focused on broadening diverse participation in CNS clinical trials. This working group, led by Sian Ratcliffe and Abhishek Pratap, has reviewed the FDA Draft Guidance and provides comments on behalf of the Society. Key contributors to this are (in alphabetical order):

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COMMENTS ON DIVERSITY ACTION PLANS TO IMPROVE ENROLLMENT OF PARTICIPANTS FROM UNDERREPRESENTED POPULATIONS IN CLINICAL STUDIES GUIDANCE FOR INDUSTRY:

General Comments

ISCTM welcomes this guidance and is encouraged that the FDA has provided recommendations to assist medical product sponsors in submitting Diversity Action Plans to increase enrollment of historically underrepresented populations in clinical studies. We offer the comments on the Agency's draft guidance to help ensure that the guidance, when finalized, reflects several ongoing challenges for sponsors, including the well-known barriers to recruitment of diverse participant cohorts and considerations for international studies and trials investigating new products for CNS disorders.

The ISCTM has some general comments for consideration listed here as well as a tabulation of line-specific textual additions or modifications for consideration in the guidance document itself.

Considerations for format and content for Diversity Action Plans
It would be helpful for the Agency to provide an illustrative example of a Diversity Action Plan (DAP) with enrollment goals disaggregated by the required categories (Race, Ethnicity, Sex and Age Group) in the guidance. ISCTM also recommends acknowledging the Diversity Action Plans may need to vary by indication. This would clarify the Agency's DAP expectations, especially for enrollment goal categories that were previously not commonly utilized by sponsors and indication-specific differences. It would also be helpful to acknowledge in this section that participants may also identify as multi-racial, and how this should be addressed when describing race categories.

Despite extensive efforts, it has long proven challenging to increase diversity in clinical trials. We request that the FDA acknowledge that an expectation to enroll study participants in complete alignment with the US prevalence or incidence of the disease may be unrealistic, given that, despite sponsors' best efforts, enrollment will continue to be affected by systemic racism, historical mistrust in clinical research (which is exacerbated for Schedule I investigational

controlled substances), healthcare inequities, and differences in health literacy. We request the Agency provide clarity on the implications of not meeting enrollment goals despite demonstrable good faith efforts, including opportunities to revisit enrollment goals where necessary and/or guidance on additional measures that might be considered. It would also be useful for the Agency to provide specific guidance on revisiting enrollment goals in the case where new epidemiology data is published during program planning or execution. Importantly, ISCTM recommends that the Agency provide feedback on implications in a timely manner to Sponsors with an opportunity to discuss, to avoiding releasing these in forums such as Advisory Committees without prior opportunity to address.

Per the draft guidance, enrollment goals should be informed by the estimated prevalence or incidence of the disease or condition. It might be important in certain CNS clinical trials (e.g., psychiatry trials) to also consider the relative population of treatment-seeking individuals – in many cases prevalence and treatment seeking populations may align, but in some conditions those who seek treatment are a subset of the overall prevalence. It is difficult to inform precise enrollment goals for each race category recommended in the draft guidance because registry data and previously published papers may have been based on different race categories. We assume, accordingly, that the Agency will be flexible in its expectations for goals based on the prevalence/incident reporting in available data sources. We also request that the Agency allow a sponsor to provide an estimated range for each subgroup instead of a single proportion. The guidance is currently focused on enrollment goals and does not comment on expected participant retention/drop-out rates. It would be beneficial for the Agency to provide insight on whether goals should be set against total diverse participants required to complete the study versus diverse patients to be recruited. Furthermore, it would be beneficial to recommend inclusion of participant retention activities in the DAP.

Additionally, given the challenges in enrolling clinical trials for rare disease therapies and the data gaps in published prevalence data, it may be helpful to include further discussion in the draft guidance on FDA's thinking regarding DAPs for rare disease therapies, including where waivers would be appropriate and/or other methods for data collection, such as real-world evidence, may be helpful.

ISCTM fully supports DAPs including enrollment goals for sex. The draft guidance sometimes uses the terms gender and sex interchangeably. It is important that these terms are used carefully throughout the guidance. It will be helpful for the final guidance to clarify whether the Agency will consider inclusion of gender (and other Sexual Orientation and Gender Identity data) to contribute to diversity enrollment goals. Sexual orientation and gender identity are relevant to many CNS disorders such as depression, other physiological disorders and access to healthcare. As noted in the draft guidance, gender identity is one area where there may be a lack of representation in clinical trials. Although there are significant social challenges, methodological considerations (e.g., data privacy), and legal questions that could complicate the collection of Sexual Orientation and Gender Identity (SOGI) data, we would suggest FDA consider soliciting broad stakeholder input, such as via a workshop, to gather best practices and considerations for the potential collection of SOGI data.

Considerations for multi-regional clinical trials

The draft guidance recommends that the DAP should comprise a general description of the sponsor's plans to study a product globally. Based on this inclusion, it would be helpful to clarify in the final version of the guidance whether the intent of this is to leverage global data to support meeting the US-driven goals where appropriate, depending on the product and disease context. For example, if a global clinical trial includes sites in Spain and Latin America, would those

participants be considered in the enrollment goals for Hispanic Ethnicity. As the definition/categorization (including terms used and the ability to capture certain data elements that are considered sensitive in some regions), the potential implications of race/ethnicity varies across different countries/regions, and race/ethnicity in different regions may be more or less affected by a given condition based on differing social determinants of health, it would be helpful to understand the expectation on sponsors in summarizing these data in the DAP.

Pharmacology Considerations
The guidance acknowledges that there are relevant factors related to the drug's pharmacology that would be clinically important in a diverse patient population. Establishing the metabolic status of a drug and potential drug interactions, earlier in the drug development program, allows sponsors to identify specific groups of patients that may be more vulnerable to either safety issues due to increased drug levels or lack of efficacy due to rapid metabolism. Metabolic status can vary with race, gender, etc., and it would be important to select relevant diversity based on the known and expected pharmacology of the drug. Because of drug metabolic profiles in different groups, it may not be possible to enroll subjects representative of the population diversity due to drug-specific demographic interactions that would jeopardize the benefit/risk profile in that subgroup. Sponsors should try to understand these metabolic factors early in the development process so better able to define target population with best benefit/risk profile and inform appropriate diversity goals.

The guidance may benefit from encouraging sponsors to establish relevant metabolic status and clinically relevant DDIs and utilize this information to establish a diversity plan that addresses potential risks in subsets of the population. The inclusion of subjects in a study should have a clear objective and provisions should be made to adjust dosing in populations that may encounter safety concerns at a fixed dose. Generally, the science and drug pharmacology should guide objective decision making regarding including populations and ensuring their safety in the clinical trial.

LINE-BY-LINE RECOMMENDED EDITS
(Original text in italics; inserted text in underline)

II. BACKGROUND

Lines 84-89
There are many reasons for challenges in enrolling diverse clinical trials. ISCTM suggests the FDA summarize the relevant literature on barriers for underrepresented populations such as access to basic medical care, mistrust of science/research, limited socioeconomic support to enable participation, as well as referencing social determinants of health.

ISCTM suggests inclusion of the proposed text and a cross-reference to the CDC definitions (either the public health gateway link or other relevant reference):
<u>Social determinants of health (SDOH) are the nonmedical factors that influence health outcomes. SDOH include economic stability, transportation availability, housing and food security, access to health care, built environment, and social connectedness and can unequally affect different populations.</u>

Lines 111-115
This background section is helpful in raising many of the areas that have contributed to challenges in achieving diverse enrollment in clinical trials. There are some additional aspects such as intensity of disease that may differ in terms of experience or expression across different

races and ethnicities, and therefore are also important to acknowledge in this section. There are also facets of disease that contribute to further mistrust in healthcare or willingness to engage in clinical trials, for example, the DSM-5 criteria of Post Traumatic Stress Disorder do not consider racial trauma to be a qualifying traumatic event.

ISCTM suggests the FDA add some further wording:
…clinical characteristics (e.g. presence of comorbidities, disease etiology, disease intensity, disease descriptors/diagnostic criteria, etc.) ….

Lines 132-133
It may be helpful to acknowledge the potential influence of variations in subgroup size or inferences made for each subgroup. Or if the intention of these is to be purely descriptive analyses, that might be helpful to state. Suggested wording on the first point below.

As applicable, FDA encourages sponsors to consider such additional factors, which may support subgroup analyses, and influence the statistical power and validity of inferences based on them, *when developing Diversity Action Plan enrollment goals*.

III. CLINICAL STUDIES REQUIRING DIVERSITY ACTION PLANS
This section partitions guidance for drugs (lines 147-149) and devices (lines 150-177) but does not include relevant guidance for drug-device combination products or explain if those follow the requirements for drugs. ISCTM suggests the FDA address what studies of drug-device combination therapies require Diversity Action Plans. This is an important consideration, as device and drug-device combination products may have instructions for use that could be challenging for some patients due to socioeconomic, educational and linguistic issues – all of which would be important to address in a Diversity Action Plan.

IV. ADDRESSING RACE, ETHNICITY, SEX, AND AGE GROUP IN DIVERSITY ACTION PLANS

Lines 187-193
ISCTM requests clarity as to whether the FDA will align expectations and terms in this guidance and the January 2024 draft guidance on the collection of race and ethnicity data with the most recent OMB's Statistical Policy Directive No. 15. If so, ISCTM asks that the FDA include a cross-reference to the OMB statistical policy directive document.

ISCTM would also find it helpful for the FDA to acknowledge and include information in this section on FDA's expectations on how data should be collected and analyzed relative to participants who identify as multi-racial.

Lines 193-200
While in many cases race- and/or ethnicity-defined populations may be genetically heterogeneous such that analysis to characterize differential effects due to pharmacogenomic variability may be difficult to discern, the Plan should begin with an assessment of any data that may indicate the potential for a medical product to have differential safety or effectiveness associated with race or ethnicity.

In particular, for drugs, covariates with known potential to affect PK and PD should be assessed in order to facilitate exposure-response analyses and to inform safe and effective dosing regimens across the intended patient population, as applicable.

ISCTM recommends that the proposed recommendations should initially focus on identifying the key variability in the drug metabolism, targets and critical drug interactions to then allow for a more informed diversity plan based on the risks. Inclusion of sub-groups can then be structured to address critical safety concerns that may arise in the diverse patient population.

ISCTM recommends additional clarification in this section in terms of how to capture the timing and decision-making based on the relevant covariates that are identified related to the drug's pharmacology in the Diversity Action Plan. It would be helpful to provide clarity that the Diversity Action Plan should prioritize subsets of the patient population that are poor/extensive metabolizers, have variations in the drug target, have comorbidities that may affect safety/efficacy, or are exposed to concomitant medication/foods/other substances that may impact drug efficacy/safety. The selection of diverse patients should consider which subgroups may have a higher prevalence of such covariates and need to be represented in the study population. The inclusion of patient subgroups should be done so with a clear scientific objective and plan for analysis of that data to address the critical question of how to identify and mitigate any safety risks and required dosing adjustments.

V. CONTENT OF THE DIVERSITY ACTION PLAN

Lines 210-211
In addition to the points FDA has included here, ISCTM suggests addition of a specific bullet point regarding specific protections that might have been included, because beyond the goal of simply increasing numbers of specific demographic groups in representation, it will be ethically imperative to be conscious of their special vulnerabilities.

the sponsor's goals for enrollment and specific protections in the clinical study*, disaggregated by race, ethnicity, sex, and age group of clinically relevant study populations,*

A. Enrollment Goals

Lines 236-240
This language establishes the requirement for a rationale, but details on the Rationale are in section B.
ISCTM suggests moving the following text to Section B:

A rationale must be provided for the proposed enrollment goals, including when such goals may deviate from the estimated prevalence or incidence of a disease or condition in the intended use population. Sponsors must provide in the Diversity Action Plan a description of the general approach and rationale, which should include methodology used to derive target enrollment goals.

Lines 252-257
It is helpful that there is text in this section that the FDA recognizes that certain development programs (e.g., rare diseases) may include a single, small pivotal study.

As enrollment in trials for rare diseases is challenging and for Breakthrough Therapy indications such goals may cause long delays to trial completion and subsequent approval for general use, ISCTM suggests the insertion of additional text:

FDA recognizes that certain development programs (e.g., rare diseases), may include a single, small pivotal study in which it may not be feasible to enroll a representative population. *Despite enrolling a representative population in that study, participant numbers may be small, potentially precluding the detection of any differences in safety and effectiveness across the study population, should they exist, or limiting the sponsor's ability to conduct a robust assessment of observed differences. However, consistent representative enrollment may provide opportunities for hypothesis generation and further study.* In extreme cases where little is known about relevant demographics for a disease, a waiver may be considered in consultation with FDA (see Section VIII a).

Lines 297-300
There have been clinical trials in drug development for diseases heavily influenced by social determinants that claim that certain racial inclusion from international locales satisfy the racial inclusion goals for the United States. ISCTM respectfully suggests additional text be added in this section:

Globally conducted clinical development programs should be designed with appropriate consideration given to differences in disease characteristics, social determinants of health, *medical practice, and available therapies when selecting foreign clinical sites and defining geographic regions.*

B. Rationale for Enrollment Goals

Lines 338-341
As social determinants of health can heavily shape risk of disease, ISCTM suggests adding the following text:

Background information necessary to understand the disease or condition for which the drug or device is being investigated, including an overview of the natural history of the disease or condition, biological risk factors and social drivers, *as well as prevalence and incidence estimates, if available.*

C. Measures to Meet Enrollment Goals

Lines 398-399, 400-421
If health equity is truly being centered, there will be explicit mechanisms for accountability. The FDA may wish to consider adding text such as:

Examples of clinical study enrollment and retention strategies may include, but are not limited to the following:

- Diverse, culturally fluent and language specific ombudsmen to address participant concerns or other forms of accountability

Lines 400-402
ISCTM respectfully submits that representation without making spaces culturally fluent and language-specific or without public transparency and accountability results in performativity in diversity action plans. This does not result in interventions that are safe and effective for diverse populations. ISCTM suggests that the FDA add the following language:

- *Implementing sustained community engagement (e.g., through community advisory boards and navigators, community health workers, patient advocacy groups, local healthcare providers, community organizations, etc.)* that is culturally fluent and language-specific with public transparency and accountability.

Lines 403-408
It is important to have Diversity Action Plans that not only encompass increasing diverse enrollment in trials but that also drive comprehensive assurances about safety and efficacy of drug development for vulnerable and disproportionately impacted populations.

ISCTM suggests additional text:

- Recruiting more representative clinical investigators and clinical staff and *providing cultural competency and proficiency training may help facilitate the building of a trusting relationship with participants, provide a helpful resource for investigators and research staff on how to engage with participants with different backgrounds, help decrease biased communication and behavioral practices, and help avoid the use of cultural generalizations and stereotypes in interactions with participants.*

Lines 414-415
Telemedicine may reduce patient burden by reducing travel time and costs, and could help support underserved patient populations in rural areas. However, ISCTM acknowledges that telemedicine might not be available to all and so consideration needs to be made to ensure this is both available and appropriate.

ISCTM suggests the below additional text:
…allowing flexible hours for study visits; allowing telehealth and telemedicine visits wherever possible or available; *reimbursement for costs incurred).*

Line 415
It is critical to avoid any financial toxicity for clinical trial participants, and therefore it would be helpful for the FDA to explicitly address this in the guidance and to include wording to ensure that reimbursements are appropriate to balance between keeping payment amounts just and fair while not unduly inducing trial participation. Reducing participant out of pocket expenses as close to zero as possible should be our collective goal, particularly in minority patient groups for whom trial-related expenses could be a barrier to participation.

ISCTM suggests inclusion of the following:
It is important to ensure that not only are participants fairly and justly reimbursed for out-of-pocket expenses, but it is also critical to ensure participants do not experience financial toxicity during the course of the study. When participants have debilitating conditions, which may necessitate both caregivers and family members to support participation in trials, it is important for additional reimbursements to be considered. Sponsors need to ensure that reimbursement is appropriate and balanced relative to the needs of the clinical trial and participant burden.

ISCTM suggests including a cross-reference to the 2018 FDA guidance for *Institutional Review Boards and Clinical Investigators* on Payment and Reimbursement to Research Subjects**.**

Lines 416-420
In addition to leveraging decentralization to support diverse enrollment, it may also be helpful for sponsors to engage clinical research sites that are based in the community, employ diverse personnel or that may be newer to clinical research. As such, it would be helpful for the FDA to acknowledge and encourage this in the guidance.

ISCTM suggests the inclusion of the text below:

<u>In addition, to improve access to clinical trial sites, sponsors should consider community-based settings and/or sites that might be newer to clinical research, with appropriate site support in place.</u>