1 May 2023

To: Food and Drug Administration, HHS

Re: Docket No. FDA-2022-D-2983

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: *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products 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, comprising 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 Sian Ratcliffe and Debra 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 THE CONSIDERATIONS FOR THE DESIGN AND CONDUCT OF EXTERNALLY CONTROLLED TRIALS FOR DRUG AND BIOLOGICAL PRODUCTS GUIDANCE FOR INDUSTRY:

General Comments

ISCTM welcomes this guidance and is encouraged that the FDA has provided recommendations to sponsors and investigators considering the use of externally controlled clinical trials to provide evidence of the safety and effectiveness of a drug product.

It is understood that these recommendations address the use of externally controlled trial outcomes in participants receiving the test treatment according to a protocol and are compared to outcomes in a group of people external to the trial who had not received the same treatment. It is also understood that these recommendations address considerations for the design and analysis of externally controlled trials to study the effectiveness and safety of drugs, including discussion of threats to the validity of trial results from potential bias, and the focus on the use of patient-level data from other clinical trials or from real-world data (RWD) sources. Further, the FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

ISCTM looks forward to the ultimate adoption of guidance that clearly advances the methodology and outlines recommendations that address the potential value of other types of controls, including historical controls, as a type of external control in a clinical trial. ISCTM does think it would be helpful to understand expectations on how data are to be used from different eras, timing, tools, and diagnostic criteria, that may be incorporated effectively with knowledge of what specific information would be expected of a sponsor. ISCTM is prepared to, and would readily participate in, further public debate to achieve this goal.

Throughout this document, additional suggestions or modifications for text are inserted in regular font after italicized draft guidance text.

I. INTRODUCTION

ISCTM appreciates FDA clarification in footnote 3 page 1, *"In this guidance, the term drug product includes both human drugs and biological products."* It was noted on a few occasions that the guidance references *"drug"* as a stand-alone term which may cause ambiguity with including biologics from the scope of the definition. For example, on line 70, *"a trial design would be able to distinguish the effect of a drug from other factors."* We respectfully encourage FDA to consider updating all "drug" as a stand-alone term in guidance to "drug product" as defined in footnote 3 page 1. Additionally, consider updating all "effect" references to "treatment effect" throughout the document. Therefore, as an example, line 70 would read, *"a trial design would be able to distinguish the* treatment *effect of a drug* product *from other factors."*

The document states in footnote 5 page 1, "*Although multiple arms may be part of the overall trial design, this guidance discusses externally controlled trials involving analysis of a single*

treatment arm and a single control arm." ISCTM is unclear regarding a single treatment arm (such as dose group) why this would apply and does not seem warranted if statistical methodology is appropriate (such as any adjustments for multiple comparisons or hierarchy).

This document clarifies FDA does not discuss using external control data to supplement a control arm in a traditional randomized controlled trial on lines 36 – 38. ISCTM suggests consideration of discussion on this topic. Generally, EMA guidelines on the clinical evaluation of medicines used for nervous system disorders. recommend including both a placebo and an active control. Use of external control for collecting data on an active product would be an efficient way to satisfy both FDA and EMA requirements.

ISCTM agrees with page 4, footnote 17. Additionally, we encourage the FDA to consider updating footnote to state more inclusive language for externally controlled trial designs in central nervous system disorders, which could be considered variable and therefore excluded based on this footnote. For example, *"Scenarios that* may not *be suitable for externally controlled trials include when the natural history of the disease of interest* may not be *understood sufficiently or when the disease course* may be *considered well-understood but* may be *variable."* As a further addition, if consideration could be given to adding language to address how choice of population in the external control arm and matching approaches can help to provide justification for external control arms, even when disorders may be variable, such as "In the advent of disease variability careful consideration needs to be given and justified based on population choice, data source, and specific matching approaches to ensure appropriate applicability of external control arm data."

ISCTM also agrees with page 4, footnote 18. *"FDA recommends that sponsors generate audit trails in their datasets that can track access to, and analyses performed on relevant data sources."* However, ISCTM suggests adding language to track reasons data may not have been used to further promote transparency for example, "*FDA recommends that sponsors generate audit trails in their datasets that can track access to, and analyses performed on relevant data sources,* including reasons certain data sources may not have been used."

II. BACKGROUND

As noted above on ISCTM's respectful request for term consistency, FDA may consider updating all "effect" references to "treatment effect" throughout the document. Therefore, as an example in this section, line 70 would read, *"a trial design would be able to distinguish the* treatment *effect of a drug* product *from other factors."*

Line 71 states*, "Importantly, before choosing to conduct a clinical trial using an external control arm as a comparator, sponsors and investigators should consider the likelihood that such a trial design would be able to distinguish the effect of a drug from other factors that impact the outcome of interest and meet regulatory requirements."* ISCTM suggests that footnote 13 reference 21 CFR 314.126 could be expanded with the specifics of the CFR section to provide context and ease of reference examples of requirements listed*. "…outcomes of interest and meet requirements* for adequate and well-controlled investigations to provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drug products.

Line 73-77 state, *"The suitability of an externally controlled trial design warrants a case-by-case assessment, informed by issues including heterogeneity of the disease (e.g., clinical presentation, severity, prognosis), preliminary evidence regarding the drug product under investigation, the approach to ascertaining the outcome of interest, and whether the goal of the trial is to show superiority or non-inferiority.".* FDA may consider updating lines to comment on the suitability of potential data sources for use as an external arm ". . . *whether the goal of the trial is to show superiority or non-inferiority,* and the suitability of alternative sources of data for an externally controlled trial."

Page 4 footnote 17 states, *"Scenarios that would not be suitable for externally controlled trials include when the natural history of the disease of interest is not understood sufficiently or when the disease course is considered well-understood but is variable."* ISCTM respectfully requests changing footnote to state "… May not *be suitable for externally controlled trials…"* thus, including many disorders in CNS, specifically psychiatric diagnoses. A sufficiently large cohort in the external control arm should capture the variability in the disease course, allowing one to draw conclusions about average disease course. Additionally, investigators may consider selecting for a more specific subgroup in a patient population to decrease this variability.

ISCTM suggests line 85 - 90 to include "or outcome measures. *"...prognostic differences in the study populations, knowledge of treatment assignment (lack of blinding), or other factors such as differences in concomitant therapies* or outcome measures."

III. DESIGN AND ANALYSIS OF EXTERNALLY CONTROLLED TRIALS

A. Design Considerations

1. Overview

Line 112 states *"...and approaches to minimize missing data and sources of bias."* ISCTM suggests adding *"...and approaches to* identify and *minimize missing data and sources of bias."* This change places an emphasis on the importance of having a full understanding of potential data characteristics. This also aligns with the language used at lines 143-146 regarding both understanding and addressing bias/confounders using analytical methods.

ISCTM requests FDA to add "including potential impact of disease heterogeneity" to the end of sentence on Line 128. *"...regarding the natural history of the disease involved and relevant prognostic factors influencing outcomes,* including potential impact of disease heterogeneity." It is important to acknowledge disease heterogeneity at all stages of the conceptualization and data selection/preparation process.

ISCTM suggests changing line 132 -133 to include co-morbidities. Co-morbid conditions can greatly impact outcomes and are often listed as exclusionary in treatment arms. Proposed language, *"From a practical perspective, fit-for-use data on suspected confounding factors (e.g., history of cigarette smoking, performance status*, co-morbidities)."

Line 145 – 146 States*, "... along with analytic methods to reduce the impact of such bias ..."* The extent of the impact of bias should include the sources and amount of bias. This is important to get a holistic view. *"... along with analytic methods to* identify, quantify and *reduce the impact of such bias…"*

2. Characteristics of Study Populations

No recommendations.

3. Attributes of Treatment

Line 200 States, *"In addition, management of treatment- or disease-related adverse events may not be predefined …"* Documentation of medical events differ from clinical practice and clinical trials. Clinicals trials document adverse events, while in clinical practice medical events are documented as side effects. Therefore, adding the expectation of identifying them is critical. ISCTM respectfully requests FDA to change line 200 to state,
"In addition, identification, documentation and *management of treatment- or disease-related adverse events may not be predefined …"*

ISCTM respectfully requests FDA to consider including a general statement regarding treatment location in Line 205. *"Examples include differences in* location of treatment (i.e., clinic vs. inpatient setting), *in health-seeking behaviors, insurance coverage …"*

ISCTM requests the FDA to consider modifying Line 212 to state, *"These and other health care delivery factors—at the level of the patient, provider, or health system—can influence treatment selection* and actual care administered." The treatment selected may be different than actual care delivered, and ideally both should be documented for appropriate analysis.

4. Designation of Index Date (Time Zero)

No recommendations.

5. Assessment of Outcomes

Line 305-306

"Whereas both trial arms would be similarly affected in a traditional randomized trial, extensive heterogeneity or substantial changes in …" Diagnostic criteria may change not only over time but may be non-uniform across different global regions therefore, ISCTM respectfully requests FDA to consider adding, "due to temporal or geographical changes" to line 306 so that is states, *"Whereas both trial arms would be similarly affected in a traditional randomized trial, extensive heterogeneity* (due to temporal or geographical changes) *or substantial changes in …"*

Line 307 *"…diagnostic criteria can introduce bias…"* ISCTM requests adding to line "or standard assessment…" Therefore, text would state, "*…diagnostic criteria can introduce bias* or standard assessment…

B. Data Considerations for the External Control Arm

1. Data from Clinical Trials

ISCTM requests the FDA to consider combining lines 339, 340 and 341 so that it will state, "A particular concern for bias would be the selection of an external control arm from a completed trial whose results of the external control arm are inconsistent with prior experience." As this provides the context and rationale for why completed trial results could introduce bias.

Line 342-343 states, *"Furthermore, when using data from other clinical trials as an external control arm, sponsors should consider the extent of and reason for any missing data and how the interpretability of study results may be affected."* ISCTM respectfully requests FDA to add, "or how it may influence the choice of outcome" to the end of the text. ISCTM's request is to make it explicit that the characteristics of the missing data from an external dataset may reflect choice of outcome. Therefore, *"Furthermore, when using data from other clinical trials as an external control arm, sponsors should consider the extent of and reason for any missing data and how the interpretability of study results may be affected,* or how it may influence the choice of outcome*."*

2. Data from RWD Sources

No recommendations.

3. Considerations for Assessing Comparability of Data Across Trial Arms

No recommendations.

Table. Summary of Considerations for Assessing Comparability of Data

Page 13
Missing data section
Consideration for Data Comparability states, *"The extent of missing data in the external control arm should be assessed before conducting an externally controlled trial to evaluate feasibility (when such data are available). When analyzing results from such a trial, the extent of missing data in both the treatment and external control arms should be assessed to examine the potential impact of missing data."*

Extent and type of missing data are both important. e.g., data that are MCAR vs MNAR for a given outcome would have very different implications for design and analysis/missingness handling. Therefore, ISCTM respectfully requests FDA consider making changes to this section to state, *"The extent and properties of missing data in the external control arm should be assessed before conducting an externally controlled trial to evaluate feasibility (when such data are available). When analyzing results from such a trial, the extent* and properties *of missing data in both the treatment and external control arms should be assessed to examine the potential impact of missing data*, and potential impacts of the type of missing data."

C. Analysis Considerations

1. General Considerations

Line 400-402 states, *"No single statistical or analytical method will be suitable for all trials involving external control arms, and potential approaches should be discussed with the appropriate FDA review division."* ISCTM requests FDA to consider adding language that external controls may be population-matched or patient-matched controls and the considerations that should be given. With added language the lines would read, *"No single statistical or analytical method will be suitable for all trials involving external control arms, and potential approaches should be discussed with the appropriate FDA review division.* Furthermore, the determination, rationale, or criteria for use of a patient-matched external control or a population-matched external control may be discussed with the division."

ISCTM respectfully requests lines 424-246 changed from, *"Especially when the anticipated effect size is modest, an externally controlled trial may not be an appropriate study design because of concerns for bias affecting the results*," to state, "Effect size should be evaluated in the context of objectivity of the primary endpoint, for example, a modest effect size on a performance-based measure may be acceptable in rare diseases with a well characterized natural history progression. progression." The rationale for suggesting this is that the current draft text may exclude a significant number of promising treatments for ultra rare conditions, where externally controlled arm trials might be most needed for viability of clinical research in these conditions, or for conditions where no treatment is available a modestly effective treatment would offer patients relief until better treatments are available.

2. Missing Data

No recommendations.

3. Misclassification of Available Data

Line 476 – 478 states, *"Although analytical modeling methods could be used to assess the potential impact of misclassification, the best strategy to avoid bias is to use objective and reliable measurements for the data of interest."* ISCTM requests FDA to consider adding language to include "strengthen subjective assessments using centralized scoring methods" and the term "valid" over *"objective and reliable".* For additional context and reasoning behind this suggestion, ISCTM provides the following case example of the assessment of radiographs (from both the retrospective natural history study and children treated with Crysvita [burosumab for the treatment of X-linked hypophosphatemia]) by the same blinded radiologist and the use of three propensity score analyses to mitigate several imbalances in the demographics (i.e., sex and baseline rickets scores) between the treatment and historical control groups.

Revised Line 476 – 478 states, "*Although analytical modeling methods could be used to assess the potential impact of misclassification, the* preferred *strategy to avoid bias* could *use* valid *measurements* to strengthen subjective assessments using centralized scoring methods *for the data of interest."*

4. Additional Analyses

No recommendations.

IV. CONSIDERATIONS TO SUPPORT REGULATORY REVIEW

A. Communication with FDA

No recommendations.

B. Access to Data and Documents

ISCTM respectfully requests FDA to consider adding language in this section that may encourage sponsors to make publicly available de-identified, patient-level data used for external control. The rationale is that this may reduce overall development costs and time and aid in the development of new therapies. Most importantly in cases of rare diseases in which no published natural history or publicly available database may be available.

GLOSSARY

No recommendations.