ISCTM
International Society for CNS Clinical Trials and Methodology

ISCTM CNS Clinical Trial Diversity WG

Friday 13 September 2024

Collating comments for Draft FDA Diversity Action Plan Guidance

Chairs: Sian Ratcliffe & Abhishek Pratap

Disclosures

Sian Ratcliffe

Head of Global Clinical Operations, Analytics, Technology & Data Sciences

Employee and shareholder of Biogen

Shareholder of Pfizer

Data presented today is not linked to any Biogen studies/trials

Opinions = mine

General Comments

- Welcoming guidance
- Providing clear intention to address disparities in clinical research
- Required at start of pivotal studies
- General expectations on content of plan clear
- Clinical trial diversity is one element of health equity - what are the implications if good faith efforts are not successful?
- Using examples would be helpful in sections to illustrate expectations

Monitoring enrollment goals

Are there clear expected data presentations?

Defining actions to take – if enrollment ambitions are not met, are there secondary actions that can be taken and are there options for FDA interaction

For global trials, can global data augment or replace data gaps in US data?

US/Global diversity

Data standards: are there expected data standards for collection, and would it be helpful to cross-ref recent CDISC guidance?

With global MRCTs, if race/ethnicity data are not routine/allowed to be captured, should this be detailed in the Diversity Action Plan?

Multiracial: if participants identify >1 race, how should this be captured and represented in data collection and analyses?

Is the intent of guidance to be very general and should the sponsor define these aspects in the Diversity Action Plan a priori

Timing and holistic aspects

- Whilst Diversity Action Plan may be reviewed specifically for pivotal programs, important that entire drug dev lifecycle considered based on early opportunities to assess gender or ethnic differences via Clin Pharm package
- For data packages leveraging AI/ML, important to understand source model data to minimize bias or data gaps
- For presentation of disaggregated data by sex, should this be adjusted for/representative of expected epidemiology?
- 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. This would clarify the Agency's DAP expectations, especially for enrollment goal categories that were previously not commonly utilized by sponsors (e.g., Sex).

Considerations regarding sex and gender

- The 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.
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- As noted in the draft guidance, gender identity is one area where we there may be a lack of representation in clinical trials. The National Institute on Minority Health and Health Disparities has identified the sexual and gender minority, or LGBTQIA+, communities as a "health disparity population". We recommend that the FDA, sponsors, and sites collaborate to explore considerations for the collection of Sexual Orientation and Gender Identity (SOGI) data. There are significant social challenges, methodological considerations (e.g., data privacy), and legal questions that could complicate this endeavor. Accordingly, we suggest the FDA consider soliciting broad stakeholder input, such as via a workshop or RFI, to gather best practices and considerations for the potential collection of SOGI data.

Epidemiology

- Per the draft guidance, enrollment goals should be informed by the estimated prevalence or incidence of the disease or condition. It is difficult to inform precise enrollment goals for each race category recommended in the draft guidance (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White) due to the fact that registry data and previously published papers may have been based on different race categories (e.g., Asian/Pacific Islander, non-Hispanic Black, and non-Hispanic White). 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.

- We recommend that FDA consider the findings of the *FDA Public Workshop on Enhancing Diversity in Therapeutics Development for Pediatric Patients* before finalizing the guidance.

- In addition, a new drug application (NDA) must present effectiveness and safety data by gender, age, and race and must identify any modifications of dose or dose interval needed for a specfic subgroup.
    - The guidance should focus on this aspect and guide on how to collect more comprehensive data earlier in the program in order to establish more thoughtful dosing regimens in phase II/III patient trials based on factors that may affect drug efficacy or safety in diverse patient subgroups. The timing of collecting this information in the drug development program is essential to address these issues proactively in phases II/III

- While in many cases race-and/or ethnicity-defined populations may be genetically heterogenous 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 ot have differential safety or effectiveness associated with race or ethnicity.
    - Guidance should address here any notable metabolic variations or variations in targeted receptors that are associated with the drug. As stated here, many of these populations are hetergenous, hence, drug risks may vastly vary in a given subset.

- 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.
    - This point is central to the guidance. It should be expanded here that these covariates should be examined as early in the program as possible to help inform appropriate patient representation and modfications to dosing to include a population that is diverse in drug response and may be more or less vulnerable to the drug effects.
    - Please expand this section to include a more structured approach to timing and decision-making based on the relevant covariates that are identified related to the drug's pharmacology. The Diversity Plan should prioritize subsets of the patient population that are poor/extensive metabolizers, have variations in the drug target, have comorbidites 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 take into account 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 rather than following a generic checklist of inclusion which may not necessarily address the critical question of how to identify and mitigate any safety risks and required dosing adjustments.