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CLIENT ALERT

FDA Develops Guidance for Enhancing the Diversity of Clinical Trial Populations

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On November 9, 2020, the U.S. Food and Drug Administration (FDA or the Agency) issued guidance intended to enhance the diversity of clinical trial populations given the litany of challenges certain underrepresented groups face participating in clinical trials. FDA's guidance recommends approaches that sponsors of clinical trials intended to support a new drug application or a biologics license application can take to increase enrollment of underrepresented populations in their clinical trials.

Specifically, FDA offers recommendations for broadening eligibility criteria, enrollment practices, and trial designs by considering both demographic characteristics of study populations (*e.g.*, sex, race, ethnicity, age, location of residency) and non-demographic characteristics of populations (*e.g.*, patients with organ dysfunction, comorbid conditions, disabilities, those at the extremes of the weight range, and populations with diseases or conditions with low prevalence).

See FDA Guidance regarding the Enhancement of Diversity in Clinical Trial Populations, *available here*.

In general, one objective of eligibility criteria is to exclude people from participating in a trial for whom the risk of an adverse event outweighs that individual's potential benefit. However, as data on excretory and metabolic pathways and drug-drug interactions become available during the drug development program, and as the safety experience with a product increases, FDA believes that eligibility criteria should be broadened to include more medically complex participants. FDA encourages sponsors to consider the following recommendations to broaden eligibility criteria in clinical trials and to ensure study populations better reflect the patient populations likely to use the drug in clinical practice:

- When developing clinical trial protocols, sponsors should work to ensure that eligibility criteria serve the goal of having a representative sample of the population for whom the drug has been developed and examine each exclusion criterion to determine if it is needed to help assure the safety of trial participants or to achieve the study objectives.
- Consider whether exclusion criteria from phase 2 studies (which may be very restrictive and are often transferred to phase 3 protocols) can be eliminated or modified for phase 3 trials, which have a different objective than phase 2 studies, to avoid unnecessary limits on the study population. It may be possible in some cases to have the

development program include specific studies in higher-risk populations conducted at sites with expertise in working with such participants.

- Sponsors should enroll participants who reflect the characteristics of clinically relevant populations with regard to age, sex, race, and ethnicity.

Likewise, sponsors should consider the below various trial design and methodological approaches that will facilitate enrollment of a broader populations:

- Consider characterizing — in early clinical development — drug metabolism and clearance across populations that may metabolize or clear the drug differently, which will help avoid later exclusions and, more generally, will allow dose adjustment to optimize effectiveness and safety across different populations.
- Use of an adaptive clinical trial design that would allow for pre-specified trial design changes during the trial when data becomes available. For example, an adaptive design can start with a narrow population if there are concerns about safety and can expand to a broader population based on interim safety data from the trial that provide support for doing so.
- Consider a broader pediatric development program early. The arbitrary sequential enrollment of pediatric subgroups by chronological age for some conditions could unnecessarily delay development of medicines for children by limiting the population for study.
- Consider including pharmacokinetic sampling to establish dosing in women who become pregnant during a trial when it is possible for continued participation with sufficient assurances of safety, and if the risks to the participant and fetus of continued trial participation are reasonable in relation to the anticipated benefits and the importance of the knowledge that may be expected to result.

Sponsors should also consider broadening eligibility criteria in trials by using enrichment strategies.[1] Enrichment may increase the trial's potential to show an effect, if one exists, by ensuring that participants have a particular severity of a disease, subset of a disease, or genetic marker. Prognostic enrichment enrolls participants who are more likely to reach study endpoints (*e.g.*, participants with risk factors for cardiovascular disease in a cardiovascular outcome trial). Predictive enrichment enrolls participants with a specific characteristic (*e.g.*, genetic) that makes them more likely to respond to an intervention.

FDA recognizes that participants may still face additional challenges to enrolling in clinical trials, including frequent visits to specific sites and financial costs. Moreover, participation in traditional trials may not be desirable for individuals under current clinical care on a regularly scheduled basis (*e.g.*, individuals with multiple chronic conditions), or for certain populations that have a mistrust of clinical research. Sponsors can improve the diversity of enrolled participants by accounting for logistical and other participant-related factors. FDA recommends several potential approaches for sponsors to do so:

- Consider reducing the frequency of study visits to those needed to appropriately monitor safety and efficacy and consider whether flexibility in visit windows is possible and whether electronic communication is appropriate. Sponsors should also consider the use of mobile medical professionals to visit participants.
- Offer and make participants aware of financial reimbursements for expenses associated with costs incurred by participation in clinical trials (*e.g.*, travel and lodging expenses).
- Implement more-inclusive strategies for public outreach and education, including incorporating patient-focused research into clinical trial design. Sponsors should consider working directly with communities to address participant needs and involve site coordinators, patients, patient advocates, and caregivers in the design of clinical trial protocols in order to determine which elements of the protocol may discourage participation and how the study can be optimally designed to enhance recruitment.
- Remain engaged with communities after the conclusion of the clinical research by sharing trial updates. Sponsors can also provide cultural competency and proficiency training for clinical investigators and research staff that 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.

- Ensure that clinical trial sites include geographic locations with a higher concentration of racial and ethnic minority patients and indigenous populations, as well as locations within the neighborhoods where these populations receive their health care.
- Make recruitment events accessible by holding them often, as well as offering them during evening and weekend hours, and in non-clinical but trusted locations.
- Consider providing trial resources and documents in multiple languages and multilingual research staff and/or interpreters in order to encourage the participation and retention of individuals with limited English comprehension.
- Consider using online/social media recruitment strategies to identify participants for whom a traditional referral center is not accessible.
- Consider using "electronic informed consent" to allow participants to read and sign necessary forms remotely instead of traveling to a clinical trial site, while ensuring that all potential participants, including those with literacy issues, understand all necessary information.

Despite sponsors' efforts to broaden inclusion criteria, there may be patients who simply do not meet the eligibility criteria or for other reasons cannot participate in the clinical trial. FDA's expanded access regulations[2] provide a pathway to patients, when they have a serious or immediately life-threatening disease or condition, to better access treatment with an investigational drug (provided certain criteria are met).

FDA recognizes that clinical trials of investigational drugs intended to treat rare diseases or conditions present a unique set of challenges, and that because rare diseases often affect small, geographically dispersed patient populations with disease-related travel limitations, special efforts may be necessary to enroll and retain these participants and ensure that a broad spectrum of the patient population is represented. Therefore, FDA offers the following additional approaches to address these issues:

- Engage early in the drug development process with patient advocacy groups, experts, and patients with the disease, and elicit their suggestions for the design of trials, including trial protocols, that participants will be willing to enroll in and support.
- Consider re-enrollment of participants in early-phase trials into later-phase randomized trials when studying the effectiveness of treatments for rare diseases. Re-enrollment should be done in limited circumstances, when medically appropriate and scientifically sound, if there is no unreasonable or anticipated safety issue, and as long as the therapy received in phase 1 is not expected to change the course of the disease.
- Make available an open-label extension study with broader inclusion criteria after early-phase studies, to encourage participation by ensuring that all study participants, including those who received a placebo, will ultimately have access to the investigational treatment.

The Agency concludes that broadening eligibility criteria and adopting more-inclusive enrollment practices should improve the quality of studies by (1) ensuring that the study population is more representative of the population that will use the drug if the drug is approved, (2) facilitating the discovery of important safety information about use of the investigational drug in patients who will take the drug after approval, and (3) increasing the ability to understand the therapy's benefit-risk profile in later stages of drug development for the phase 3 population across the patient population likely to use the drug in clinical practice.

We note that government orders on the local, state, and federal levels are changing every day, and the information contained herein is accurate only as of the date set forth above.

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For further information or questions on FDA's guidance, please contact Amandeep S. Sidhu, T. Reed Stephens, Christopher Parker, or your Winston relationship attorney.

[1] Enrichment is a trial design strategy in which there is a targeted inclusion of certain populations, with the goal of more readily demonstrating the effect, if any, of the drug.

[2] Expanded access refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain the kind of information about the drug that is generally derived from clinical trials.

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