Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2020
Clinical/Medical

participants[5] with a wide range of baseline characteristics may create a study population that more accurately reflects the patients likely to take the drug if it is approved and allow assessment of the impact of those characteristics on the safety and effectiveness of the study drug.

In issuing this guidance, FDA is satisfying the mandate under section 610(a)(3) of the FDA Reauthorization Act of 2017 (FDARA) (21 U.S.C. 360bbb note).[6] Consistent with the FDARA mandate, this guidance discusses (1) broadening eligibility criteria and avoiding unnecessary exclusions for clinical trials; (2) developing eligibility criteria and improving trial recruitment so that the participants enrolled in trials will better reflect the population most likely to use the drug, if the drug is approved, while maintaining safety and effectiveness standards; and (3) applying the recommendations for broadening eligibility criteria to clinical trials of drugs intended to treat rare diseases or conditions.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BROADENING ELIGIBILITY CRITERIA TO INCREASE DIVERSITY IN ENROLLMENT

One objective of eligibility criteria is to exclude people from participating in a trial for whom the risk of an adverse event outweighs both that individual's potential benefit from participating and the importance of the knowledge that may be expected to result.[7] FDA recognizes that certain exclusions are appropriate when necessary to help protect such individuals. For example,

Medically complex patients with certain concomitant illnesses or those taking particular drugs may also be excluded in drug development programs. Such patients may be more susceptible to a potential toxicity of the investigational drug and can experience adverse events that are related to their underlying conditions or concomitant treatments (i.e., a participant's current medications interact with the investigational drug), which may impact their ability to complete the trial or meet all of the trial obligations.

As data on excretory and metabolic pathways and drug-drug interactions become available during the drug development program, allowing appropriate dose adjustments, there should be fewer exclusions related to concomitant medications or comorbidities. Similarly, as the safety experience with a product increases, eligibility criteria should be broadened to include more medically complex participants, an-6.1(i)TJ 0.t..15 Th2(or)3(e)4( )]r3(ea)-6(s)2(o)-6(n)2(a)-6(bl)2(e)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(pa)-6(r)3(t)-6(i)2(c)-6(i)2(p)-6(a)2(n)-6(t)2(s)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(w)-6(h)2(o)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(ha)-6(v)2(e)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(a)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(pa)-6(r)3(t)-6(i)2(c)-6(u)2(l)-6(a)2(r)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(d)-6(r)3(u)-6(g)2(s)-6(,)]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(m)-6(a)2(y)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(b)-6(e)2( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(m)-6(o)2(r)-6(e)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(s)-6(u)2(s)-6(c)2(e)-6(p)2(t)-6(i)2(b)-6(l)2(e)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(t)-6(o)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(a)-6(d)2(v)-6(e)2(r)-6(s)2(e)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(e)-6(v)2(e)-6(n)2(t)-6(s)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(t)-6(h)2(a)-6(t)2( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(a)-6(r)3(e)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(r)3(e)-6(l)2(a)-6(t)2(e)-6(d)2( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(t)-6(o)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(t)-6(h)2(e)-6(i)2(r)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(u)-6(n)2(d)-6(e)2(r)-6(l)2(y)-6(i)2(n)-6(g)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(c)-6(o)2(n)-6(d)2(i)-6(t)2(i)-6(o)2(n)-6(s)2( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(o)-6(r)3( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(c)-6(o)2(n)-6(c)2(o)-6(m)2(i)-6(t)2(a)-6(n)2(t)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(t)-6(r)3(e)-6(a)2(t)-6(m)2(e)-6(n)2(t)-6(s)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(\()-6(i)2(.)-6(e)2(.)-6(,)]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(a)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(p)-6(a)2(r)-6(t)2(i)-6(c)2(i)-6(p)2(a)-6(n)2(t)-6(')]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(s)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(c)-6(u)2(r)-6(r)3(e)-6(n)2(t)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(m)-6(e)2(d)-6(i)2(c)-6(a)2(t)-6(i)2(o)-6(n)2(s)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(i)-6(n)2(t)-6(e)2(r)-6(a)2(c)-6(t)2( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(w)-6(i)2(t)-6(h)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(t)-6(h)2(e)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(i)-6(n)2(v)-6(e)2(s)-6(t)2(i)-6(g)2(a)-6(t)2(i)-6(o)2(n)-6(a)2(l)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(d)-6(r)3(u)-6(g)2(,)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(w)-6(h)2(i)-6(c)2(h)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(m)-6(a)2(y)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(i)-6(m)2(p)-6(a)2(c)-6(t)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(t)-6(h)2(e)-6(i)2(r)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(a)-6(b)2(i)-6(l)2(i)-6(t)2(y)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(t)-6(o)2( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(c)-6(o)2(m)-6(p)2(l)-6(e)2(t)-6(e)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(t)-6(h)2(e)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(t)-6(r)3(i)-6(a)2(l)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(o)-6(r)3( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(m)-6(e)2(e)-6(t)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(a)-6(l)2(l)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(o)-6(f)2( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(t)-6(h)2(e)-6( )]TJ 0 -1.2 TD 0.0003 Tc 0.0003 Tw [(t)-6(r)3(i)-6(a)2(l)-6( )]TJ 0 -1.2 TD 0 Tc 0 Tw [(o)-6(b)2(l)-6(i)2(g)-6(a)2(t)-6(i)2(o)-6(n)2(s)-6(.)]TJ 0 -1.2 TD

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- When developing clinical trial protocols, 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

issues), or interactions between these factors.[19] Analyzing data on race and ethnicity may assist in identifying population-specific signals.[20] Therefore, FDA recommends that for drugs and biologics, sponsors include a plan for inclusion of clinically relevant populations no later than the end of the Phase 2 meeting.[21]

III. OTHER STUDY DESIGN AND CONDUCT CONSIDERATIONS FOR IMPROVING ENROLLMENT

As noted previously

participants at their locations instead of requiring participants to visit distant clinical trial sites.

- During recruitment, 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). FDA does not consider reimbursement for reasonable travel expenses to and from the clinical trial site and associated costs such as airfare, parking, and lodging to raise issues regarding undue influence.[28] Similarly, consideration may be gis5 >>BD 0 Tw3.

strengthen bi-directional relationships with communities. Providing cultural competency and proficiency training for clinical investigators and research staff 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 bias and communication and behavioral practices, and help avoid the use of cultural generalizations and stereotypes in interactions with participants. Understanding how participants choose whether to participate in a clinical trial allows sponsors to more effectively recruit participants who may be reluctant to enroll.

- Ensure that clinical trial sites include geographic locations with a high concentration of racial and ethnic minority patients and indigenous populations, as well as locations within the neighborhoods where these populations receive their health care, because [illegible]

- Consider using real-world data to promote more efficient recruitment of a diverse population by using, for example, claims data and electronic health records (while maintaining patient privacy and ensuring that patient permissions/consent for the sharing/access of identifiable data from electronic health records is obtained and maintained) to identify potential sites and participants.[33]

- Consider use of 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.[34] Underrepresented populations with limited or no internet access, however, may benefit from personal interactions with investigators to better understand the risks and benefits of trial participation; for these populations, consider holding consenting processes and interventions in locations that are more accessible to the participant.

C. Expanded Access

Despite efforts to broaden inclusion criteria, there may be patients who do not meet the eligibility criteria or for other reasons cannot participate in the clinical trial. 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.[35] 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. However, in certain limited circumstances, data from expanded access use may inform clinical development (e.g., by identifying patients for subsequent studies).[36]

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[33] For additional discussion on the use of real-world data in study planning and recruitment, see Clinical Trials Transformation Initiative (CTTI) Recommendations: Use of Real-World Data to Plan Eligibility Criteria and Enhance Recruitment, available at https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/rwd-recommendations_final.pdf. For more information on FDA's real-world data program, see Framework for FDA's Real-World Evidence Program, available at https://www.fda.gov/media/120060/download.

[34] See the guidance for institutional review boards, investigators, and sponsors, Use of Electronic Informed Consent in Clinical Investigations — Questions and Answers (December 2016). As used in that guidance document, electronic informed consent refers to the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive websites, biological recognition devices, and card readers to convey information related to the study and to obtain and document informed consent.

[35] See 21 CFR part 312, subpart I, Expanded Access to Investigational Drugs for Treatment Use.

[36] See question 26 in the guidance for industry Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers (October 2017).

including those who received placebo, will ultimately have access to the

- In June 1993, within the global pharmaceutical regulatory community (ICH), (of which FDA is a member), issued a guideline titled Studies in Support of Special Populations: Geriatrics E7, which discourages arbitrary maximum age requirements in clinical trial protocols and encourages the inclusion of participants with concomitant illness and those receiving concomitant medications, many of whom are often older adults.[4]

- In February 2012, an ICH guidance for industry, adopted by FDA, clarified ICH E7 and emphasizes the importance of including older adult patients in clinical trials, especially patients 75 years or older.[5]

- In 2014 in the FDASIA Action Plan, FDA reiterated support for efforts to include older adult patients in clinical trials.[6]

3. Inclusion of Pregnant Women

- In 2016, section 2041[7] of the 21st Century Cures Act[8] required the establishment of a Task Force on Research Specific to Pregnant Women and Lactating Women. The task force was charged with providing advice and guidance to the Secretary of Health and Human Services on Federal activities related to identifying and addressing gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women.[9]

- In April 2018, FDA published a draft guidance for industry on scientific and ethical considerations for inclusion of pregnant women in clinical trials.[10]

[4] The 1993 ICH guideline is available at https://database.ich.org/sites/default/files/E7_Guideline.pdf. See also the ICH guidance for industry E7 Studies in Support of Special Populations: Geriatrics (August 1994) and E7 Studies in Support of Special Populations: Geriatrics — Questions & Answers (February 2012).

[5] See ICH E7 Studies in Support of Special Populations: Geriatrics — Questions and Answers.

[6] Ibid.

[7] 42 U.S.C. 289a-2, 130 Stat. 1033, 1070.

[8]

- In May 2019, FDA issued two draft guidances providing trial design recommendations for postapproval pregnancy safety studies[11] and for clinical lactation studies.[12]

4. Inclusion of Participants with Rare Diseases

- In January 2019, FDA reissued a draft guidance on scientific considerations in drug development for rare diseases that includes suggestions for inclusion criteria and trial designs.[13]

[11] See the draft guidance for industry Postapproval Pregnancy Safety Studies (May 2019). When final, this guidance will represent FDA's current thinking on this topic.

[12] See the draft guidance for industry Clinical Lactation Studies:

APPENDIX B: CURRENT EFFORTS TO IM