Enhancing Participation in Clinical Trials — 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)

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Enhancing Participation in Clinical Trials — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry[1]

I. INTRODUCTION

Over the past few decades, FDA has promoted enrollment practices that would lead to clinical trials that better reflect the population most likely to use the drug if the drug is approved, primarily through broadening eligibility criteria.[2] Despite these efforts, challenges to participation in clinical trials remain, and certain groups continue to be underrepresented in many clinical trials. This guidance recommends approaches that sponsors of clinical trials intended to support a new drug application[3] or a biologics license application can take to increase enrollment of a representative population in their clinical trials.[4]

This guidance considers 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). Enrolling

[1] This guidance has been prepared by the Office of Medical Policy and the Office of New Drugs in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *eligibility criteria* refers to the requirements for entry into a clinical trial, i.e., the characteristics the participants must or must not have to be able to participate in the study (often referred to as inclusion and exclusion criteria). Eligibility criteria are determined for each study and generally include evidence that a participant has the disease or condition being treated, often for a defined minimum duration, defined severity, and with particular symptoms or signs, and may also include characteristics such as age, sex, medical history, current health status, presence or absence of certain genotypes, blood pressure or other physiologic parameter, and absence of certain diseases.

[3] This guidance applies to drugs, including biological products. For the purposes of this guidance, *drug* or *drug product* is used to refer to human drugs and human biological products that are regulated as drugs.

[4] This guidance applies broadly to all types of drug products, including drugs for the treatment of serious and life-threatening conditions or diseases for which there is an unmet medical need.

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 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, patients with varying degrees of kidney or liver impairment are often excluded early in drug development programs because adequate information is not available on how to adjust doses of the investigational drug for such patients or whether such patients could be more vulnerable to certain risks. Pregnant and lactating women are also frequently excluded when there is inadequate information to assess the risk to the fetus or infant.[8]

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[5] For the purposes of this guidance, the term *participant* refers to either an individual currently enrolled in a clinical trial or an individual who may potentially enroll in a clinical trial.

[6] On April 16, 2018, as mandated by section 610(a)(1) of FDARA, 131 Stat. 1005, Public Law 115-52 (August 18, 2017), FDA held a public meeting to discuss topics related to eligibility criteria in clinical trials, including (1) the rationale for, and potential barriers created by, inclusion and exclusion criteria; (2) the benefit to appropriate study populations from trials with alternative designs; (3) barriers to clinical trial participation; (4) clinical trial designs that increase trial enrollment; (5) how changes to trial inclusion and exclusion criteria could impact clinical trials; and (6) how changes to eligibility criteria may impact the complexity and length of clinical trials. Discussions at the public meeting informed this guidance.

[7] *See* 21 CFR 56.111(a)(2).

[8] For FDA's draft considerations on how and when to include pregnant women in clinical trials, s*ee* the draft guidance for industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018). When final, this guidance will represent FDA's current thinking on this topic. We update guidances

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; any remaining exclusions should be justified.

FDA also recognizes that some eligibility criteria have become commonly accepted over time or used as a template across trials, sometimes excluding certain populations from trials without strong clinical or scientific justification (e.g., older adults, those at the extremes of the weight range, those with malignancies or certain infections such as HIV, and children). Some patients may be unable to participate without reasonable accommodations (e.g., patients with physical and/or mental disabilities, non-English speakers, patients who work and require evening or weekend hours, and some older adult patients with limited access to transportation). Unnecessary exclusion of such participants may lead to a failure to discover important safety information about use of the investigational drug in patients who will take the drug after approval. Therefore, broadening eligibility criteria in later stages of drug development for the phase 3 population increases the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice.

For more information on current FDA and International Council for Harmonisation (ICH) policy initiatives on broadening eligibility criteria in clinical trials, see Appendix A.

A. Trial Practices

There are many approaches a sponsor should take to broaden eligibility criteria in clinical trials to ensure that the study population better reflects the patient population likely to use the drug in clinical practice. FDA provides the following recommendations and encourages sponsors to consider other FDA recommendations as appropriate:[9]

- 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

periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[9] *See* the following three guidances for industry regarding eligibility criteria of certain populations in oncology trials: (1) *Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections* (July 2020); (2) *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020); and (3) *Cancer Clinical Trial Eligibility Criteria: Brain Metastases* (July 2020).

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. If it is not needed, consider eliminating or modifying the criterion to expand the study population. For example, when exclusions are necessary because participants with impaired organ function would be placed at unreasonable risk, base the exclusions on an appropriately specific measure of organ dysfunction that does not lead to the unnecessary exclusion of participants with milder dysfunction.[10] For example, if there are unreasonable risks to participants with advanced heart failure, but enrollment of those with milder disease would be appropriate, the exclusion criteria should specifically define the population of heart failure participants that should be excluded (e.g., New York Heart Association (NYHA) stage III and IV).

- 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. Although excluding certain patients may be scientifically or clinically justified under specific circumstances (e.g., certain drug-drug or drug-disease interactions or concerns regarding a population's vulnerability to a particular toxicity), such criteria may be removed or modified during study conduct based upon data available from the completion of other relevant studies (e.g., *in vitro* or *in vivo* drug-drug or drug-disease interaction studies). It may also 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 (although in such a case the consent form should identify this increased risk among certain participants and the trial should be designed with the needs of the higher risk populations in mind, if the drug is intended for that population).

- Sponsors should enroll participants who reflect the characteristics of the intended-use population with regard to age, sex, race, and ethnicity. Inadequate participation and/or data analyses from a representative population can lead to insufficient information pertaining to medical product safety and effectiveness for product labeling. This objective can be met through:

  - Inclusion of children and adolescents in confirmatory clinical trials involving adults when appropriate[11, 12]

[10] *See* 21 CFR 56.111(a)(2).

[11] For considerations regarding the inclusion of adolescents in adult oncology clinical trials, see the guidance for industry *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials* (March 2019).

[12] For considerations regarding the inclusion of pediatric patients in adult oncology clinical trials, see the guidance for industry *Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients* (July 2020).

- Inclusion of women in clinical trials in adequate numbers to allow for analysis by sex, for example, by avoiding unjustified exclusion based on sex and taking other actions to promote participation.[13] For most drugs, representatives of both sexes should be included in clinical trials in numbers adequate to allow detection of clinically significant sex-related differences in drug response.[14]

- Inclusion of underrepresented racial and ethnic groups in clinical trials and the analysis of clinical trial data by race and ethnicity. Differences in response to medical products (e.g., pharmacokinetics, efficacy, or safety) have been observed in racially and ethnically distinct subgroups of the U.S. population. These differences may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors.[15] Analyzing data on race and ethnicity may assist in identifying population-specific signals.[16]

B. Trial Design and Methodological Approaches

Sponsors should consider various trial design and methodological approaches that will facilitate enrollment of a broader population. The following are examples of approaches to consider:

- Consider characterizing — in early clinical development — drug metabolism and clearance across populations that may metabolize or clear the drug differently (e.g., older adults and participants with liver or kidney dysfunction). Early characterization of drug metabolism and clearance across groups will help avoid later exclusions and, more generally, will allow dose adjustment to optimize effectiveness and safety across different populations.

- Using an adaptive clinical trial design would allow for pre-specified trial design changes during the trial when data become available, including altering the trial population.[17] 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. Adaptive trials may also provide for broader enrollment when there is uncertainty regarding whether the drug will be

[13] *See* the guidance for industry *Study and Evaluation of Sex Differences in the Clinical Evaluation of Drugs* (July 1993).

[14] Ibid. For more information regarding FDA's policy on understanding sex differences and the inclusion of women in clinical trials, see "Understanding Sex Differences at FDA," available at https://www.fda.gov/consumers/about-owh/sex-biological-variable, and "Women in Clincal Trials: Research and Policy," available at https://www.fda.gov/consumers/women-clinical-trials/women-clinical-trials-research-and-policy.

[15] *See* Huang SM and Temple R, 2008, Is this the drug or dose for you? Impact and consideration of ethnic factors in global drug development, regulatory review, and clinical practice, Clin Pharmacol Ther, 84(3):287–294.

[16] Ibid.

[17] *See* the guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* (November 2019).

safe and effective in certain populations, with an interim analysis that will enable adjustment of future enrollment based on pre-specified criteria regarding response.

- 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. Therefore, staggering enrollment in pediatric studies based on chronological age (i.e., enrollment of older pediatric participants first, then younger pediatric participants) should be justified with a clear scientific rationale (e.g., a known or potential developmental safety concern).[18]

- 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. This may provide important information regarding drug metabolism during pregnancy and across the trimesters, a time when physiology can change significantly.

C. Broadening Eligibility Criteria in Trials Using Enrichment Strategies

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.[19] 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) or who have a disease of greater severity, reducing the size of a trial necessary to show an effect. Predictive enrichment enrolls participants with a specific characteristic (e.g., genetic, pathophysiologic) that makes them more likely to respond to an intervention. In general, enrichment should not lead to the exclusion of demographic groups; even with enrichment, efforts to maintain enrollment criteria that are as broad and representative as possible are important.

Enrichment strategies can increase the ability of a trial to detect an effect of the investigational drug; however, it is sometimes advisable to include a reasonable sample of marker-negative participants who have the disease but do not meet the enrichment criteria, particularly when (1) there is uncertainty about the sensitivity of the measurement for the enrichment marker and the responsiveness of marker-negative patients and (2) substantial use is anticipated in the marker-

[18] For more information on the inclusion of pediatric subpopulations, *see* the ICH guidance for industry *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018).

[19] *See* the guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* (March 2019). This guidance defines enrichment as "the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population."

negative population (e.g., for serious diseases with few alternative therapies). Apart from enrichment-based selection criteria, the unnecessary use of exclusions described previously should be avoided.

As noted, even in an enriched trial, it may be useful to include a broader participant group. These participants could be part of a secondary analysis of efficacy, perhaps with a different efficacy endpoint (e.g. a surrogate marker). Enrolling participants across the full spectrum of disease severity should be considered, even if the primary endpoint is based on a population with a particular stage of the disease. This approach allows the study to utilize enrichment to help demonstrate effectiveness and may also, if adequately designed, provide some efficacy information on the broader population.

III. OTHER STUDY DESIGN AND CONDUCT CONSIDERATIONS FOR IMPROVING ENROLLMENT

As noted previously, beyond the limitations in participation imposed by narrow eligibility criteria, potential participants may face additional challenges to enrolling in clinical trials. A trial requiring participants to make frequent visits to specific sites may result in added burden for participants, especially older adults, children, disabled and cognitively impaired individuals who require transportation or caregiver assistance, or participants who live far from research facilities, such as those in rural or remote locations. Financial costs (e.g., travel, missing work, dependent care) may also impede participation, and study visits may interfere with jobs and/or family and community obligations. Moreover, for individuals under current clinical care on a regularly scheduled basis (e.g., individuals with multiple chronic conditions), additional clinical trial study visits may be psychologically, physically, and financially burdensome, and a disincentive for enrollment. A mistrust of clinical research among certain populations also impacts enrollment.[20] FDA, the National Institutes of Health, and HHS have a number of resources that serve to further the goal of improving enrollment practices and broadening eligibility criteria. (See Appendix B.)

As part of the overall study design, sponsors can improve the enrollement of participants by accounting for logistical and other participant-related factors that could limit participation in clinical trials. The following are a few examples of potential approaches, and FDA encourages the development of other approaches.

A. Make Trial Participation Less Burdensome for Participants

- During the study design phase, consider the recruitment challenges that may occur because of the planned visit schedule and difficulties with accessibility (including for individuals with disabilities) to trial sites: reduce 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

[20] For more discussion on barriers to clinical trial enrollment, see the "Public Workshop: Evaluating Inclusion and Exclusion Criteria in Clinical Trials," held April 16, 2018, available at https://www.fda.gov/media/134754/download.

communication (e.g., telephone/mobile telephone, secured electronic mail, social media platforms) or digital health technology tools[21] can be used to replace site visits and provide investigators with adequate real-time data.[22] Consider the use of mobile medical professionals, such as nurses and phlebotomists, to visit 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.[23] Similarly, consideration may be given to paying participants in exchange for their participation in research. FDA recognizes, however, that payment for participation may raise difficult questions that should be addressed by the IRB, such as how much money participants should receive, and for what participants should receive payment, such as their time, inconvenience, discomfort, or some other consideration.[24]

B. Adopt Enrollment and Retention Practices That Enhance Participation

- Implement various strategies for public outreach and education, including incorporating patient-focused research into clinical trial design.[25] Industry, patient advocacy groups, medical associations, and other stakeholders can consider collaborating to educate participants about clinical trial participation. Work 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. Patients may provide valuable insight into challenges and burdens and may be more willing to accept risk for a potential benefit from participation or to further knowledge about their disease; however, reasonably foreseeable risks

[21] For the purposes of this guidance, a *digital health technology tool* is a sensor, a device, or a device component that detects and measures a physical or chemical characteristic and translates this into an electrical signal. Digital health technology tools are generally capable of transmitting the information they record from study participants to remote databases (e.g., ambulatory blood pressure monitor).

[22] *See* the guidance for industry *Use of Electronic Health Record Data in Clinical Investigations* (July 2018), which provides recommendations on the use of electronic health record data in FDA-regulated clinical investigations.

[23] *See* the information sheet guidance for institutional review boards and clinical investigators *Payment and Reimbursement to Research Subjects* (January 2018). *See also* 21 CFR 50.20.

[24] Ibid.

[25] *See* the guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collective Comprehensive and Representative Input* (June 2020).

must be communicated to participants in the documents provided as part of obtaining informed consent. *See* 21 CFR 50.25(a)(2).

- Consider fostering community engagement through medical societies, focus groups, community advisory boards, disease registries, and community-based participatory research, the latter of which promotes the design of clinical research with the assistance of community members and leaders to more effectively meet the needs of potential participants.[26] Remain engaged with communities after the conclusion of the clinical research and share trial updates to continue to 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 biased 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 higher concentration of underrepresented racial and ethnic patients and indigenous populations, as well as locations within the neighborhoods where these populations receive their health care, because restricting clinical trial sites to selected geographic locations may limit the ability to enroll a representative population. Consider selecting health care providers and study coordinators who also reflect the demographics of participants to assist with clinical trial recruitment, because participants may prefer a health care provider who they can relate to.

- Make recruitment events accessible by holding them often, as well as offering them during evening and weekend hours. Consider holding the events in non-clinical but trusted locations (such as places of worship or community centers), social commercial venues (such as barbershops and beauty salons), and public events (such as cultural festivals, carnivals, and parades) as a means of connecting with different populations and populations that may have limited or no internet access.

- Explore agreements to facilitate the exchange of medical records between clinical trial sites in order to promote participant retention by obtaining participant consent for clinical trial investigators to transfer medical records, including electronic medical records, when participants move from one location to another, because participants often struggle to navigate the gathering and transfer of records between sites.

[26] https://www.nimhd.nih.gov/research/extramural-research/community-health-and-population-science.

- 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 real-world data to promote more efficient recruitment of trial participants 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.[27]

- 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.[28] 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 eligibility 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.[29] 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

[27] For additional discussion on the use of real-world data in study planning and recruitment, *see* the web page Clinical Trials Transformation Initiative (CTTI) Recommendations: Use of Real-World Data to Plan Eligibility Criteria and Enhance Recruitment, available at https://ctti-clinicaltrials.org/about/ctti-projects/real-world-data/ctti-recommendations-use-of-real-world-data-to-plan-eligibility-criteria-and-enhance-recruitment. 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.

[28] *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.

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

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).[30]

IV. BROADENING ELIGIBILITY CRITERIA AND ENCOURAGING RECRUITMENT FOR CLINICAL TRIALS OF INVESTIGATIONAL DRUGS INTENDED TO TREAT RARE DISEASES OR CONDITIONS

Clinical trials of investigational drugs intended to treat rare diseases or conditions present a unique set of challenges. Because of limited numbers of patients, maximum participation in clinical trials is essential for successful trial completion and interpretation. 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 to ensure that a broad spectrum of the patient population is represented.

Although certain strategies, including predictive and prognostic enrichment, are used to increase the efficiency of clinical trials for rare diseases, the effects in the broader population remain of interest. Sponsors should therefore consider the following additional approaches (and others as appropriate) to broadening clinical trial eligibility criteria for clinical trials of investigational drugs intended to treat rare diseases and improve the enrollment and retention of participants with rare diseases:

- 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. For a number of rare diseases, there are active patient advocacy groups that are strongly committed to finding new therapies and supporting clinical trials.

- 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 anticipated safety issue, and as long as the therapy received in phase 1 is not expected to change the course of the disease. Traditionally, participants are often considered ineligible for a phase 3 trial if they had been previously exposed to the drug in the earlier-phase trial; however, with so few patients available for rare disease trials, re-enrolling participants may be reasonable and may facilitate the analysis of safety and efficacy in the broadest possible population. Sponsors considering this approach should examine the potential for selection bias as the participants who better tolerated the drug and experienced more effectiveness in early phases may be disproportionally selected for a phase 3 trial, which may contribute to safety findings that are not representative of the population of patients who will use the drug if it is approved. The safety and

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

tolerability profile observed in the entire study population and the percent of reenrolled participants in the phase 3 trial, taken together, can help to inform the degree to which selection bias would likely contribute to the overall assessment of safety and tolerability.

- 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 placebo, will ultimately have access to the investigational treatment.

V. CONCLUSION

Broadening eligibility criteria and optimizing enrollment practices should improve the quality of studies by ensuring that the study population is more representative of the population that will use the drug if the drug is approved; by facilitating the discovery of important safety information about use of the investigational drug in patients who will take the drug after approval; and by 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. FDA encourages sponsors to consider the approaches outlined in this guidance and develop other approaches as appropriate.

APPENDIX A: CURRENT EFFORTS TO BROADEN ELIGIBILITY CRITERIA IN CLINICAL TRIALS

The Food and Drug Administration (FDA) and the International Council for Harmonisation (ICH) have issued a number of population-specific guidances to address the importance of encouraging broad participation in clinical trials and avoiding unnecessary exclusions:

1. Clinically Relevant Populations

- In 2013, FDA broadly addressed eligibility criteria with its good review practice document titled *Good Review Practice: Clinical Review of Investigational New Drug Applications* that guides its clinical reviewers to examine investigational new drug protocols for unwarranted exclusions.[1]

- In 2014, FDA published an action plan titled *FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data* (FDASIA Action Plan) in response to the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA).[2] The FDASIA Action Plan proposes strategies to encourage greater clinical trial participation, including collaborating with industry, other federal agencies, and interested stakeholders to improve clinical trial participation.

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2. Older Adult Populations

- In November 1989, FDA articulated its support for the participaton of older adults in clinical trials with the release of a guidance for industry titled *Guideline for the Study of Drugs Likely to be Used in the Elderly*.

- 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 participation of individuals wth concomitant illness and those receiving concomitant medications, many of whom are often older adults.[3]

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[1] *See* "Good Review Practice: Clinical Review of Investigational New Drug Applications," available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM377108.pdf.

[2] *See* the "FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data," available at https://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/UCM410474.pdf.

[3] The 1993 ICH guideline is available at https://database.ich.org/sites/default/files/E7_Guideline.pdf. *See also* the ICH guidances 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).

- In February 2012, an ICH guidance for industry, adopted by FDA, clarifies ICH E7 and encourages the participation of older adults jin clinical trials, especially patients 75 years or older. [4]

- In 2014 in the FDASIA Action Plan, FDA reiterated support for efforts to include older adult patients in clinical trials.[5]

3. Pregnant Women

- In 2016, section 2041[6] of the 21st Century Cures Act[7] 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.[8]

- In April 2018, FDA published a draft guidance for industry on scientific and ethical considerations for inclusion of pregnant women in clinical trials.[9]

- In May 2019, FDA issued two draft guidances providing trial design recommendations for postapproval pregnancy safety studies[10] and for clinical lactation studies.[11]

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

[5] Ibid.

[6] 42 U.S.C. 289a-2, 130 Stat. 1033, 1070.

[7] 130 Stat. 1033, Pub. L. 114-255 (January 6, 2016).

[8] *See* 42 U.S.C. 289a-2; *see also* https://www.nichd.nih.gov/about/advisory/PRGLAC. The task force developed recommendations to address areas such as overcoming participation barriers for pregnant women and lactating women and integrating them into the research agenda. *See* the task force final report to the HHS Secretary and Congress, September 2018, available at https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf.

[9] *See* the draft guidance for industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018). When final, this guidance will represent FDA's current thinking on this topic.

[10] *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.

[11] *See* the draft guidance for industry *Clinical Lactation Studies: Considerations for Study Design* (May 2019). When final, this guidance will represent FDA's current thinking on this topic.

4. Participants with Rare Diseases

- In January 2019, FDA reissued a draft guidance on scientific considerations on drug development for rare diseases that includes suggestions for eligibility criteria and trial designs.[12]

[12] *See* the guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023).

APPENDIX B: CURRENT EFFORTS TO IMPROVE PARTICIPATION IN CLINICAL TRIALS

The following is a sampling of efforts by the Food and Drug Administration (FDA), the Department of Health and Human Services, and the National Institutes of Health (NIH) to improve enrollment practices in clinical trials:

- FDA's Office of Women's Health provides information and resources for researchers on participation of women in clinical trials, including webinars, videos, scientific workshop proceedings, and links to other relevant resources.[13]

- The Office for Human Research Protections at the Department of Health and Human Services provides resources and information for the public on clinical trial participation, including informational videos and links to other federal websites and media articles.[14]

- NIH informs the public about the availability of clinical trials and how to enroll through its website "NIH Clinical Research Trials and You."[15]

- The website clinicaltrials.gov, maintained by the NIH National Library of Medicine, provides a database with information on publicly and privately supported clinical studies that is accessible to the public and health care providers.[16]

- ResearchMatch, a public clinical research registry partially funded by NIH's National Center for Advancing Translational Sciences, connects researchers with people who are interested in participating in clinical trials.[17]

[13] "Women in Clinical Trials," available at https://www.fda.gov/science-research/womens-health-research/fda-research-policy-and-workshops-women-clinical-trials.

[14] "About Research Participation," available at https://www.hhs.gov/ohrp/education-and-outreach/about-research-participation/index.html.

[15] "NIH Clinical Research Trials and You," available at https://www.nih.gov/health-information/nih-clinical-research-trials-you.

[16] https://clinicaltrials.gov/ct2/home

[17] https://www.researchmatch.org.