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# Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry

## *DRAFT GUIDANCE*

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For questions regarding this draft document, contact (CDER) Ebla Ali-Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

**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)**

**June 2019  
Clinical/Medical**

# Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry

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1 **Enhancing the Diversity of Clinical Trial Populations — Eligibility**  
2 **Criteria, Enrollment Practices, and Trial Designs**  
3 **Guidance for Industry<sup>1</sup>**  
4

5  
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
10 for this guidance as listed on the title page.  
11

12  
13  
14  
15 **I. INTRODUCTION**  
16

17 Over the past few decades, FDA policy initiatives have focused on promoting enrollment  
18 practices that lead to clinical trials better reflecting the population most likely to use the drug if  
19 the drug is approved, primarily through broadening eligibility criteria.<sup>2</sup> Despite these efforts,  
20 challenges to participation in clinical trials remain, and certain groups continue to be  
21 unnecessarily underrepresented in many clinical trials. This guidance recommends approaches  
22 that sponsors of clinical trials to support a new drug application<sup>3</sup> or a biologics license  
23 application can take to broaden eligibility criteria, when scientifically and clinically appropriate,  
24 and increase enrollment of underrepresented populations<sup>4</sup> in their clinical trials.<sup>5</sup>  
25

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<sup>1</sup> This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

<sup>2</sup> For the purposes of this guidance, the term *eligibility criteria* refers to the requirements for entry into a clinical trial that describe the characteristics the participants must or must not have to be able to participate in the study (i.e., inclusion and exclusion criteria). Eligibility criteria are determined for each study and may include, for example, characteristics such as age, gender, medical history, current health status, presence or absence of certain genotypes, blood pressure, heart rate, and absence of certain diseases.

<sup>3</sup> This guidance applies to drugs, including biological drug 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.

<sup>4</sup> This guidance applies to both demographic populations (e.g., sex, race, ethnicity, age) and non-demographic populations (e.g., patients with organ dysfunction, comorbid conditions, and those at the extremes of the weight range).

<sup>5</sup> 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.

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26 FDA is issuing this guidance to satisfy the mandate under section 610(a)(3) of the FDA  
27 Reauthorization Act of 2017 (FDARA) (21 U.S.C. 360bbb note).<sup>6</sup> In accordance with the  
28 FDARA mandate, this guidance discusses (1) broadening eligibility criteria and avoiding  
29 unnecessary exclusions for clinical trials; (2) developing eligibility criteria and improving trial  
30 recruitment so that the participants<sup>7</sup> enrolled in trials will better reflect the population most likely  
31 to use the drug, if the drug is approved, while maintaining safety and effectiveness standards;  
32 and (3) applying the recommendations for broadening eligibility criteria to clinical trials for  
33 drugs intended to treat rare diseases or conditions.

34  
35 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
36 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
37 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
38 the word *should* in Agency guidances means that something is suggested or recommended, but  
39 not required.

### **II. BROADENING ELIGIBILITY CRITERIA TO INCREASE DIVERSITY IN ENROLLMENT**

44  
45 One objective of eligibility criteria is to help protect participants by excluding people for whom  
46 the risk of an adverse event from participation is not likely to be reasonable in relation to any  
47 potential benefit and the importance of the knowledge that may be expected to result.<sup>8</sup> For  
48 example, patients with decreased renal function or certain concomitant illnesses are often  
49 excluded because of concerns that they may be more susceptible to the adverse effects of an  
50 investigational drug because it is metabolized by the kidney or interacts with other medications  
51 the patient takes.

52  
53 In addition, participants with multiple concomitant illnesses and those receiving other drugs are  
54 often excluded because of concerns that such conditions or other drugs could affect a  
55 determination of the investigational drug’s safety or effectiveness. Pregnant women are also  
56 frequently excluded out of concern for fetal health. In addition to protecting participant safety,  
57 the exclusion of certain patients on multiple medications or with multiple comorbidities is  
58 sometimes intended to avoid noise in the safety data. Medically complex patients often have  
59 adverse clinical events that are related to their underlying conditions, which may make it difficult

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<sup>6</sup> On April 16, 2018, as mandated by section 610(a)(1) of FDARA, 131 Stat. 1005, Public Law 115-52 (Aug. 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 population diversity; (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.

<sup>7</sup> 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.

<sup>8</sup> See 21 CFR 56.111(a)(2).

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60 to determine whether the adverse event is related to the investigational drug, to the medical  
61 condition, or to a concomitant treatment.

62  
63 At the same time, certain populations are often excluded from trials without strong clinical or  
64 scientific justification (e.g., the elderly, those at the extremes of the weight range, individuals  
65 with organ dysfunction, those with malignancies or certain infections such as HIV, and children).  
66 Additionally, failure to include complex participants in a development program may lead to a  
67 failure to discover important safety information about use of the investigational drug in patients  
68 who will take the drug after approval. Therefore, broadening eligibility criteria, when  
69 appropriate, maximizes the generalizability of trial results and the ability to understand the  
70 therapy's benefit-risk profile across the patient population likely to use the drug in clinical  
71 practice, without jeopardizing patient safety.

72  
73 For more information on current FDA and International Conference on Harmonisation (ICH)  
74 policy initiatives on broadening eligibility criteria in clinical trials, see Appendix A.

### **A. Broadening Eligibility Criteria in Enriched Clinical Trials**

75  
76  
77  
78 Enrichment is a trial design strategy in which there is a targeted inclusion of certain  
79 populations, with the goal of more readily demonstrating the effect of the drug, if there is one.<sup>9</sup>  
80 Enrichment may increase the trial's potential to show an effect, if one exists, by ensuring that  
81 participants have a particular severity of a disease, a particular subset of a disease, or particular  
82 genetic markers. Prognostic enrichment enrolls participants who are more likely to reach study  
83 endpoints (e.g., participants with risk factors for cardiovascular disease in a cardiovascular  
84 outcome trial) or to have a disease of greater severity, reducing the size of a trial necessary to  
85 show an effect. Predictive enrichment includes participants with a specific characteristic (e.g.,  
86 genetic, pathophysiologic) who may be more likely to respond to an intervention. Enrichment  
87 does not usually exclude demographic groups.

88  
89 FDA encourages the use of enrichment strategies to increase the potential of a trial to detect an  
90 effect of the investigational drug, although it is often advisable to include a reasonable sample of  
91 participants who have the disease but do not meet the prognostic or predictive enrichment  
92 characteristics prespecified in the clinical trial.

93

---

<sup>9</sup> See the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* (December 2012). 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.” When final, this guidance will represent FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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94 **B. FDA Recommendations**

95

96 *1. Inclusive Trial Practices*

97

98 Sponsors should adopt practices for determining eligibility criteria that will allow the clinical  
99 trial population to reflect the diversity of the patients who will be using the drug if the drug is  
100 approved. Although there are many approaches a sponsor can take to broaden eligibility criteria  
101 in clinical trials, FDA provides the following recommendations and encourages the use of others  
102 as appropriate:<sup>10</sup>

103

104 • Examine each exclusion criterion to determine if it is needed to help assure the safety  
105 of trial participants or to achieve the study objectives when developing clinical trial  
106 protocols. If not, consider eliminating or modifying the criteria to expand the study  
107 population as well as tailoring the exclusion criteria as narrowly as possible to avoid  
108 unnecessary limits to the study population. For example, if there are unreasonable  
109 risks to participants with advanced heart failure, but enrollment of those with milder  
110 disease would be appropriate, the exclusion criteria should specifically define the  
111 population of heart failure participants that should be excluded (e.g., New York Heart  
112 Association (NYHA) stage III and IV).

113

114 • Consider whether criteria from phase 2 studies — which may be more restrictive and  
115 are often transferred to phase 3 protocols — can be eliminated or modified to avoid  
116 unnecessary limits on the study population. Although excluding certain participants  
117 may be scientifically or clinically justified under specific circumstances (e.g., certain  
118 drug-drug or drug-disease interactions or concerns regarding a population's  
119 vulnerability to a particular toxicity), such criteria may be removed or modified  
120 during study conduct based upon data available from the completion of other relevant  
121 studies (e.g., drug-drug or drug-disease interaction studies). It may be possible in  
122 some cases to have the development program include specific studies in higher risk  
123 populations conducted at sites with expertise in working with such participants  
124 (although in such a case the consent form should identify this increased risk among  
125 certain participants).

126

127 • Base exclusions on an appropriate measure of organ dysfunction that does not lead to  
128 the unnecessary exclusion of certain populations when such exclusions are necessary  
129 because participants with impaired organ function would be placed at unreasonable  
130 risk.<sup>11</sup>

131

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<sup>10</sup> See the following three draft guidances for industry regarding eligibility criteria of certain populations in oncology trials: (1) *Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, and Hepatitis C Virus Infections* (March 2019); (2) *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (March 2019); and (3) *Cancer Clinical Trial Eligibility Criteria: Brain Metastases* (March 2019). When final, these guidances will represent FDA's current thinking on these topics.

<sup>11</sup> See 21 CFR 56.111(a)(2).

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132 • Consider including children (ages 2 to 11 years) and adolescents (ages 12 to 17 years)  
133 in confirmatory clinical trials involving adults when appropriate.<sup>12, 13</sup>

134

### 135 2. *Trial Design and Methodological Approaches*

136

137 Sponsors may consider various trial design and methodological approaches to enrolling a broader  
138 population. The following are examples of potential approaches to consider:

139

140 • Consider characterizing — in early clinical development — drug metabolism and  
141 clearance across populations that may metabolize or clear the drug differently (e.g.,  
142 the elderly and patients with liver or kidney dysfunction). Early characterization of  
143 drug metabolism and clearance across groups will help avoid later exclusions.  
144 Alternatively, an expansion cohort may also allow dose modification and may be  
145 used to assess a reasonably safe dose in specific populations in which there may be  
146 significant differences in the systemic exposure to the investigational drug (e.g.,  
147 pediatric or elderly participants or participants with organ impairment).<sup>14</sup>

148

149 • Consider using adaptive clinical trials, which allow for pre-specified trial design  
150 changes during the trial, including altering the trial population.<sup>15</sup> An adaptive design  
151 can start with a narrow population if there are concerns about safety and can expand  
152 to a broader population based on interim data from the trial as well as external data.  
153 Adaptive trials may also provide for broader enrollment when there is uncertainty  
154 regarding whether the drug will be effective in certain populations, with an interim  
155 analysis that will enable adjustment of future enrollment based on pre-specified  
156 criteria regarding response.

157

158 • Consider a pediatric development program early (although enrollment of children and  
159 adolescents in development programs is a complex subject that is beyond the scope of  
160 this guidance). For pediatric trials with potential safety concerns, consider staggering  
161 enrollment based on age (i.e., enrollment of older pediatric participants first, then  
162 younger pediatric participants). Because this approach may not always be warranted,

---

<sup>12</sup> 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).

<sup>13</sup> For considerations regarding the inclusion of pediatrics in adult oncology clinical trials, see the draft guidance for industry *Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients* (March 2019). When final, this guidance will represent FDA's current thinking on this topic.

<sup>14</sup> See the draft guidance for industry *Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics* (August 2018). This draft guidance defines a first-in-human (FIH) multiple expansion cohort trial as an FIH trial with a single protocol with an initial dose-escalation phase that also contains three or more additional patient cohorts with cohort-specific objectives. When final, this guidance will represent FDA's current thinking on this topic.

<sup>15</sup> See the draft guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (September 2018). When final, this guidance will represent FDA's current thinking on this topic.



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163 such enrollment should be justified with a clear scientific rationale (e.g., juvenile  
164 toxicity studies have not yet been completed to support studies in younger pediatric  
165 participants).<sup>16</sup>  
166

- 167 • Consider including a broader participant group in the trial as part of the secondary  
168 efficacy and safety analyses, even when the primary analysis population is narrowed  
169 (e.g., when using enrichment designs). Consider enrolling participants across the full  
170 spectrum of disease severity, and structure eligibility criteria to include participants  
171 from all disease stages or syndrome presentations, while assessing efficacy and safety  
172 for the larger population, even if the primary endpoint is based on a population with a  
173 particular stage of the disease. This approach allows the study to utilize enrichment  
174 to help demonstrate effectiveness while also providing information on effectiveness  
175 and safety in a broader population and not decreasing the chances of achieving  
176 success on the primary clinical endpoint.  
177
- 178 • Consider including pharmacokinetic sampling when appropriate and when it is  
179 possible for continued participation with sufficient assurances of safety during  
180 pregnancy to establish dosing in women who become pregnant during a trial and in  
181 whom the risks of continued trial participation are reasonable in relation to the  
182 anticipated benefits and the importance of the knowledge that may be expected to  
183 result. This may provide important information regarding drug metabolism during  
184 pregnancy and across the trimesters, a time when physiology can change  
185 significantly.  
186

### **188 III. OTHER STUDY DESIGN AND CONDUCT CONSIDERATIONS FOR 189 IMPROVING ENROLLMENT**

190  
191 Beyond the limitations in participation imposed by narrow eligibility criteria, potential  
192 participants may face additional challenges to enrolling in clinical trials. A trial requiring  
193 participants to make frequent visits to specific sites may result in added burden for participants,  
194 especially the elderly, children, disabled and cognitively impaired individuals who require  
195 transportation or caregiver assistance, or participants who live far from research facilities, such  
196 as those in rural or remote locations. Burdensome financial costs (e.g., travel, missing work)  
197 may also impede participation, and study visits may interfere with jobs and/or family and  
198 community obligations. Moreover, for individuals under current clinical care on a regularly  
199 scheduled basis (e.g., individuals with multiple chronic conditions), additional clinical trial study  
200 visits may be burdensome and a disincentive for enrollment in clinical trials. A mistrust of  
201 clinical research among certain populations also impacts enrollment.<sup>17</sup> FDA, the National

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<sup>16</sup> See the ICH guidance for industry *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018).

<sup>17</sup> 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/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCA/FDARA/ucm598050.htm>.

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202 Institutes of Health (NIH), and HHS have a number of resources that serve to further the goal of  
203 improving enrollment practices and broadening inclusion criteria. (See Appendix B)

204  
205 As part of the overall study design, sponsors can improve the diversity of enrolled participants by  
206 accounting for logistical and other participant-related factors that could limit participation in  
207 clinical trials. The following are a few examples of potential approaches, and FDA encourages  
208 the development of other approaches.

### **A. Make Trial Participation Less Burdensome for Participants**

- 211  
212 • During the study design phase, consider the recruitment challenges that may occur  
213 because of the planned visit schedule: reduce the frequency of study visits to  
214 those needed to appropriately monitor safety and efficacy and consider whether  
215 flexibility in visit windows is possible and whether electronic communication  
216 (e.g., telephone/mobile telephone, secured electronic mail, social media  
217 platforms) or mobile technology tools<sup>18</sup> can be used to replace site visits and  
218 provide investigators with real-time data.<sup>19</sup>  
219
- 220 • During recruitment, offer and make participants aware of financial  
221 reimbursements for expenses associated with costs incurred by participation in  
222 clinical trials (e.g., travel and lodging expenses). FDA does not consider  
223 reimbursement for reasonable travel expenses to and from the clinical trial site  
224 and associated costs such as airfare, parking, and lodging to raise issues regarding  
225 undue influence.<sup>20</sup> Similarly, consideration may be given to paying participants  
226 in exchange for their participation in the research; however, FDA recognizes that  
227 payment for participation may raise difficult questions that should be addressed  
228 by the IRB, such as how much money should participants receive, and for what  
229 should participants receive payment, such as their time, inconvenience,  
230 discomfort, or some other consideration.<sup>21</sup>  
231

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<sup>18</sup> For the purposes of this guidance, a *mobile 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. Mobile technology tools are generally capable of transmitting the information they record from study participants to remote databases (e.g., ambulatory blood pressure monitor).

<sup>19</sup> 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.

<sup>20</sup> See the guidance for institutional review boards and clinical investigators *Payment and Reimbursement to Research Subjects — Information Sheet* (January 2019), available at <https://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm>. See also 21 CFR 50.20.

<sup>21</sup> Ibid.

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- 232           **B.     Adopt Enrollment and Retention Practices That Enhance Inclusiveness**  
233
- 234           • Work directly with communities to address participant needs and to involve  
235           patients, patient advocates, and caregivers in the design of clinical trial protocols.  
236           Patients may provide valuable insight into challenges and burdens and may be  
237           more willing to accept risk for a potential benefit as long as the risks are clearly  
238           communicated in the informed consent and the research team explains the risks.  
239           Community-based participatory research promotes the design of clinical research  
240           with the assistance of community members and leaders to more effectively meet  
241           the needs of potential participants.<sup>22</sup> Understanding how participants choose  
242           whether to participate in a clinical trial allows sponsors to more effectively recruit  
243           participants who may be reluctant to enroll.  
244
  - 245           • Ensure that clinical trial sites include geographic locations with a higher  
246           concentration of racial and ethnic minority patients to recruit a more diverse study  
247           population. Consider diversity when selecting health care providers to assist with  
248           clinical trial recruitment because this may promote diversity among participants.<sup>23</sup>  
249
  - 250           • Incorporate strategies for public outreach and education. Industry, patient  
251           advocacy groups, medical associations, and other stakeholders can consider  
252           collaborating to educate participants about clinical trial participation.  
253
  - 254           • Make recruitment events accessible by holding them often, as well as offering  
255           them during evening and weekend hours. Consider holding the events in non-  
256           clinical but trusted locations (such as houses of worship) and social commercial  
257           venues (such as barbershops and beauty salons) as a means of connecting with  
258           diverse populations.  
259
  - 260           • Explore agreements to foster the exchange of medical records between clinical  
261           trial sites in order to promote participant retention by obtaining participant  
262           consent for clinical trial investigators to transfer medical records, including  
263           electronic medical records, when participants move from one location to another,  
264           because participants often struggle to navigate the gathering and transfer of  
265           records between sites.  
266

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<sup>22</sup> <https://www.nimhd.nih.gov/programs/extramural/community-based-participatory.html>.

<sup>23</sup> Racial and ethnic minorities currently comprise a small percentage of clinical trial participants relative to the prevalence of disease in these populations. According to the Zip Code Analysis Project, 80 percent of minorities live in only 20 percent of the zip codes in the United States. See “Dialogues on Diversifying Clinical Trials: Successful Strategies for Engaging Women and Minorities in Clinical Trials,” available at <https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM334959.pdf>.

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### 267 **C. Expanded Access**

268  
269 Despite efforts to broaden inclusion criteria, there may be patients who do not meet the eligibility  
270 criteria or for other reasons cannot participate in the clinical trial. FDA’s expanded access  
271 regulations provide a pathway to potentially offer such patients, when they have a serious or  
272 immediately life-threatening disease or condition, treatment with an investigational drug,  
273 provided certain criteria are met, including that there is no comparable or satisfactory alternative  
274 therapy.<sup>24</sup> Expanded access refers to the use of an investigational drug when the primary  
275 purpose is to diagnose, monitor, or treat a patient’s disease or condition rather than to obtain the  
276 kind of information about the drug that is generally derived from clinical trials. However, in  
277 certain limited circumstances, data from expanded access use may inform clinical  
278 development.<sup>25</sup>

### 279 280 281 **IV. BROADENING ELIGIBILITY CRITERIA AND ENCOURAGING** 282 **RECRUITMENT FOR CLINICAL TRIALS OF INVESTIGATIONAL DRUGS** 283 **INTENDED TO TREAT RARE DISEASES OR CONDITIONS**

284  
285 Clinical trials of investigational drugs intended to treat rare diseases or conditions present a  
286 unique set of challenges. Because of limited numbers of patients, maximum participation in  
287 clinical trials is essential for successful trial completion and interpretation. Subsets of potential  
288 participants are sometimes excluded from clinical trials because of narrow eligibility criteria,  
289 including (1) those with advanced disease or without narrowly defined symptoms in a  
290 heterogenous disorder, (2) age, (3) duration of disease, (4) severity of symptoms, (5)  
291 concomitant medication, or (6) disability. Because rare diseases often affect small,  
292 geographically dispersed patient populations with disease-related travel limitations, special  
293 efforts may be necessary to enroll and retain these participants to ensure that a broad spectrum of  
294 the patient population is represented.

295  
296 Although certain strategies, including predictive and prognostic enrichment, are used to increase  
297 the efficiency of clinical trials for rare diseases, the effects in the broader population remain of  
298 interest.

299  
300 Sponsors should therefore consider the following approaches (and others as appropriate) to  
301 broadening clinical trial eligibility criteria for clinical trials of investigational drugs intended to  
302 treat rare diseases and improve the enrollment and retention of participants with rare diseases:

- 303  
304
  - Engage early in the drug development process with patient advocacy groups that are  
305 strongly committed to finding new therapies, to elicit their suggestions for the design  
306 of trials, including trial protocols, that participants will be willing to enroll in and  
307 support. For a number of rare diseases, there are active patient advocacy groups that  
308 are strongly committed to finding new therapies and supporting clinical trials.

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<sup>24</sup> See 21 CFR part 312, subpart I, Expanded Access to Investigational Drugs for Treatment Use.

<sup>25</sup> See question 26 in the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers* (June 2016; updated October 2017).

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- Plan to re-enroll participants from early-phase trials into later-phase trials when studying the effectiveness of treatments for rare diseases — in limited circumstances, if medically appropriate, and if there is no unreasonable anticipated safety issue. Traditionally, participants are often ineligible for a phase 3 trial if they had been previously exposed to the drug in an earlier-phase trial; however, with so few participants in rare disease trials, re-enrolling participants may facilitate the analysis of safety and efficacy in the broadest possible population. Caution should be exercised to avoid selection bias, as the participants who better tolerated the drug and experienced more effectiveness in early phases may be disproportionately selected for a phase 3 trial, which may contribute to efficacy findings that are not representative of the larger population that will use the drug if the drug is approved.
- Make available an open-label extension study 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 adopting more inclusive enrollment practices will open clinical trials to a diverse participant population reflective of the population that will use the drug if the drug is approved. To avoid unnecessary exclusions and obtain critical safety and effectiveness data applicable to a more representative patient population, sponsors should consider the recommendations in this guidance when designing and conducting clinical trials. FDA also encourages sponsors to consider and develop other approaches as appropriate.

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### 337 **APPENDIX A: CURRENT EFFORTS TO BROADEN ELIGIBILITY CRITERIA IN** 338 **CLINICAL TRIALS**

339  
340 The Food and Drug Administration (FDA) and the International Conference on Harmonisation  
341 (ICH) have issued a number of population-specific guidances to address the need to include a  
342 broad population in clinical trials and avoid unnecessary exclusions:

#### 343 344 **1. Inclusion of Clinically Relevant Populations**

- 345  
346 • In 2013, FDA broadly addressed inclusion criteria with its good review practice  
347 document titled *Good Review Practice: Clinical Review of Investigational New Drug*  
348 *Applications* that guides its clinical reviewers to examine investigational new drug  
349 protocols for unwarranted exclusions.<sup>1</sup>
- 350  
351 • In 2014, FDA published an action plan titled *FDA Action Plan to Enhance the*  
352 *Collection and Availability of Demographic Subgroup Data* (FDASIA Action Plan)  
353 in response to the 2012 Food and Drug Administration Safety and Innovation Act  
354 (FDASIA).<sup>2</sup> The FDASIA Action Plan proposes strategies to encourage greater  
355 clinical trial participation, including collaborating with industry, other federal  
356 agencies, and interested stakeholders to improve clinical trial diversity.
- 357  
358 • In 2016, prompted by the FDASIA Action Plan, FDA published the guidance titled  
359 *Collection of Race and Ethnicity Data in Clinical Trials*, which encourages sponsors  
360 to enroll participants who reflect the demographics of clinically relevant populations  
361 with regard to age, gender, race, and ethnicity, and recommends that sponsors submit  
362 a plan to address the inclusion of clinically relevant populations to the Agency.<sup>3</sup>

#### 363 364 **2. Inclusion of Elderly Populations**

- 365  
366 • In November 1989, FDA articulated its support for the inclusion of elderly  
367 participants in clinical trials with the release of a guidance for industry titled  
368 *Guideline for the Study of Drugs Likely to be Used in the Elderly*.
- 369  
370 • In June 1993, within the global pharmaceutical regulatory community, ICH (of which  
371 FDA is a member) issued a guideline titled *Studies in Support of Special Populations*:

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<sup>1</sup> See “Good Review Practice: Clinical Review of Investigational New Drug Applications,” available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM377108.pdf>.

<sup>2</sup> See the “FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data,” available at <https://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCA/t/FDASIA/UCM410474.pdf>.

<sup>3</sup> See the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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372 *Geriatrics E7*, which discourages arbitrary maximum age requirements in clinical  
373 trial protocols and encourages the inclusion of participants with concomitant illness  
374 and those receiving concomitant medications, many of whom are often elderly.<sup>4</sup>  
375

376 • In February 2012, an ICH guidance for industry, adopted by FDA, clarifies ICH E7  
377 and emphasizes the importance of including elderly patients in clinical trials,  
378 especially patients 75 years or older.<sup>5</sup>  
379

380 • In 2014 in the FDASIA Action Plan, FDA reiterated support for efforts to include  
381 elderly patients in clinical trials.<sup>6</sup>  
382

### 3. Inclusion of Women

383  
384  
385 • In July 1993, FDA issued a guidance titled *Guideline for the Study and Evaluation of*  
386 *Gender Differences in the Clinical Evaluation of Drugs*, which discourages  
387 unjustified exclusion based on gender in clinical trials.<sup>7</sup> FDA encourages the  
388 inclusion of women in clinical trials and the analysis of clinical trial data by gender,<sup>8</sup>  
389 which reflects good drug development practice and provides better health information  
390 for both genders across demographic groups.<sup>9</sup>

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<sup>4</sup> The 1993 ICH guideline is available at

[http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E7/Step4/E7\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Step4/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).

<sup>5</sup> See ICH *E7 Studies in Support of Special Populations: Geriatrics – Questions and Answers*.

<sup>6</sup> *Ibid.*

<sup>7</sup> See the guidance for industry [*Guideline for the*] *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* (July 1993).

<sup>8</sup> Although the terms sex and gender have sometimes been used interchangeably in scientific literature and health policy, FDA guidance and regulations (*see, e.g.*, 21 CFR 312.33(a)(2) and 314.50(d)(5)(v)) address the reporting and analysis of clinical trial data by gender. FDA also supports the analyses of data by sex, with sex defined as a biological construct and gender as a social construct in accordance with the 2001 Institute of Medicine (IOM) report (*see* Wizeman, TM and Pardue, M (Eds.), 2001, *Exploring the Biological Contributions to Human Health: Does Sex Matter?* National Academies Press). Analyzing data by sex allows researchers to determine if there are any sex differences impacting health conditions and treatment options across the continuum of life stages and can provide insight into the scientific basis for individual therapy differences. Likewise, FDA's guidance for industry [*Guideline for the*] *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* encourages the inclusion of women in clinical trials, to evaluate potential variation in treatment effects due to biological differences between genders.

<sup>9</sup> Although FDA recognizes the unique terms of sex and gender as defined by the 2001 IOM report (*see* *ibid.*), for the purposes of this guidance, the term *women* refers to participants' biological construct. 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/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm131182.htm>, and "FDA

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- In 2016, Section 2041<sup>10</sup> of the 21st Century Cures Act,<sup>11</sup> 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.<sup>12</sup> The task force convened from August 2017 to May 2018 and developed recommendations to address areas such as building research infrastructure and networks and overcoming participation barriers for pregnant women and lactating women.<sup>13</sup>
  - In April 2018, FDA published a draft guidance for industry on scientific and ethical considerations for inclusion of pregnant women in clinical trials.<sup>14</sup>
  - In May 2019, FDA issued two draft guidances providing trial design recommendations for postapproval pregnancy safety studies<sup>15</sup> and for clinical lactation studies.<sup>16</sup>

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Research, Policy, and Workshops on Women in Clinical Trials,” available at <https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm131731.htm>.

<sup>10</sup> 42 U.S.C. 289a-2, 130 Stat. 1033, 1070.

<sup>11</sup> 130 Stat. 1033, Pub. L. 114-255 (Jan. 6, 2016).

<sup>12</sup> See 42 U.S.C. 289a-2; see also <https://www.nichd.nih.gov/about/meetings/2017/082117>.

<sup>13</sup> 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](https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf).

<sup>14</sup> 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.

<sup>15</sup> 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.

<sup>16</sup> 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.



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### 408 **APPENDIX B: CURRENT EFFORTS TO IMPROVE ENROLLMENT IN CLINICAL** 409 **TRIALS**

410  
411 The following is a sampling of efforts by the Food and Drug Administration (FDA), the  
412 Department of Health and Human Services (HHS), and the National Institutes of Health (NIH) to  
413 improve enrollment practices in clinical trials:

- 414  
415 • FDA maintains a Consumer Update web page that provides general information on  
416 clinical trials for consumers, including information on clinical trial participation and  
417 informed consent.<sup>1</sup>  
418
- 419 • FDA’s Office of Minority Health provides a web page for minority consumers that  
420 contains a clinical trial diversity tool kit, a webinar, multilingual fact sheets, videos,  
421 and links to relevant resources.<sup>2</sup>  
422
- 423 • The HHS Office for Human Research Protections provides resources and information  
424 for the public on clinical trial participation, including informational videos and links  
425 to other federal websites and media articles.<sup>3</sup>  
426
- 427 • NIH informs the public about the availability of clinical trials and how to enroll  
428 through its website “NIH Clinical Research Trials and You.”<sup>4</sup>  
429
- 430 • The website [clinicaltrials.gov](https://clinicaltrials.gov), maintained by the NIH National Library of Medicine,  
431 provides a database with information on publicly and privately supported clinical  
432 studies that is accessible to the public and health care providers.<sup>5</sup>  
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<sup>1</sup> “Inside Clinical Trials: Testing Medical Products in People,” available at <https://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm>.

<sup>2</sup> “Minorities in Clinical Trials,” available at <https://www.fda.gov/ForConsumers/ByAudience/MinorityHealth/ucm472295.htm>.

<sup>3</sup> “About Research Participation,” available at <https://www.hhs.gov/ohrp/education-and-outreach/about-research-participation/index.html>.

<sup>4</sup> “NIH Clinical Research Trials and You,” available at <https://www.nih.gov/health-information/nih-clinical-research-trials-you>. For more information on NIH efforts to improve clinical trial enrollment, see “Proceedings of the NIH Workshop on the Enrollment and Retention of Participants in NIH-funded Clinical Trials,” available at [https://osp.od.nih.gov/wp-content/uploads/2015/04/Proceedings%20of%20the%202014%20NIH%20Workshop%20on%20Enrollment%20in%20NIH%20Funded%20Clinical%20Trials%20\(2\)\\_UPDATED\\_2015%20\(2\).pdf](https://osp.od.nih.gov/wp-content/uploads/2015/04/Proceedings%20of%20the%202014%20NIH%20Workshop%20on%20Enrollment%20in%20NIH%20Funded%20Clinical%20Trials%20(2)_UPDATED_2015%20(2).pdf).

<sup>5</sup> <https://clinicaltrials.gov/ct2/home>

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- 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.<sup>6</sup>

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<sup>6</sup> <https://www.researchmatch.org/>