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

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Guidance for Industry

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Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry[1]

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I. INTRODUCTION

Over the past few decades, FDA policy initiatives have focused on promoting enrollment practices that lead to clinical trials better reflecting 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 unnecessarily underrepresented in many clinical trials. This guidance recommends approaches that sponsors of clinical trials to support a new drug application[3] or a biologics license application can take to broaden eligibility criteria, when scientifically and clinically appropriate, and increase enrollment of underrepresented populations[4] in their clinical trials.[5]

[1] 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.

[2] 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.

[3] 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.

[4] 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).

[5] 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.

FDA is issuing this guidance to satisfy the mandate under section 610(a)(3) of the FDA Reauthorization Act of 2017 (FDARA) (21 U.S.C. 360bbb note).[6] In accordance 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[7] 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 for 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 help protect participants by excluding people for whom the risk of an adverse event from participation is not likely to be reasonable in relation to any potential benefit and the importance of the knowledge that may be expected to result.[8] For example, patients with decreased renal function or certain concomitant illnesses are often excluded because of concerns that they may be more susceptible to the adverse effects of an investigational drug because it is metabolized by the kidney or interacts with other medications the patient takes.

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

[6] 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.

[7] 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.

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

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.
75
76 **A. Broadening Eligibility Criteria in Enriched Clinical Trials**
77
78 Enrichment is a trial design strategy in which a 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.[9]
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

[9] *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.

B. FDA Recommendations

1. Inclusive Trial Practices

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

- Examine each exclusion criterion to determine if it is needed to help assure the safety of trial participants or to achieve the study objectives when developing clinical trial protocols. If not, consider eliminating or modifying the criteria to expand the study population as well as tailoring the exclusion criteria as narrowly as possible to avoid unnecessary limits to the study population. 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 criteria from phase 2 studies — which may be more restrictive and are often transferred to phase 3 protocols — can be eliminated or modified to avoid unnecessary limits on the study population. Although excluding certain participants 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., drug-drug or drug-disease interaction studies). It may be possible in some cases to have the development program include specific studies in higher risk populations conducted at sites with expertise in working with such participants (although in such a case the consent form should identify this increased risk among certain participants).

- Base exclusions on an appropriate measure of organ dysfunction that does not lead to the unnecessary exclusion of certain populations when such exclusions are necessary because participants with impaired organ function would be placed at unreasonable risk.[11]

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[10] *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.

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

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.[12, 13]
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).[14]
148
149 • Consider using adaptive clinical trials, which allow for pre-specified trial design
150 changes during the trial, including altering the trial population.[15] 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,

[12] 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).

[13] 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.

[14] *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.

[15] *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.

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).[16]
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
187
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.[17] FDA, the National

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

[17] 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/SignificantAmendmentstotheFDCAct/FDARA/ucm598050.htm.

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.
209
210 **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[18] can be used to replace site visits and
218 provide investigators with real-time data. [19]
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.[20] 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.[21]
231

[18] 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 and are generally capable of transmitting the information they record from study participants to remote databases (e.g., ambulatory blood pressure monitor).

[19] *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.

[20] *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.

[21] Ibid.

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.[22] 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.[23]
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

[22] https://www.nimhd.nih.gov/programs/extramural/community-based-participatory.html.

[23] 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.

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.[24] 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.[25]

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. Subsets of potential participants are sometimes excluded from clinical trials because of narrow eligibility criteria, including (1) those with advanced disease or without narrowly defined symptoms in a heterogenous disorder, (2) age, (3) duration of disease, (4) severity of symptoms, (5) concomitant medication, or (6) disability. 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 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 that are strongly committed to finding new therapies, to 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.

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

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

- 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 disproportionally 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.

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

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

1. Inclusion of Clinically Relevant Populations

- In 2013, FDA broadly addressed inclusion 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 diversity.

- In 2016, prompted by the FDASIA Action Plan, FDA published the guidance titled *Collection of Race and Ethnicity Data in Clinical Trials*, which encourages sponsors to enroll participants who reflect the demographics of clinically relevant populations with regard to age, gender, race, and ethnicity, and recommends that sponsors submit a plan to address the inclusion of clinically relevant populations to the Agency.[3]

2. Inclusion of Elderly Populations

- In November 1989, FDA articulated its support for the inclusion of elderly participants 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:*

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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] *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.

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.[4]
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.[5]
379
380 • In 2014 in the FDASIA Action Plan, FDA reiterated support for efforts to include
381 elderly patients in clinical trials.[6]
382
383 **3. Inclusion of Women**
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.[7] FDA encourages the
388 inclusion of women in clinical trials and the analysis of clinical trial data by gender,[8]
389 which reflects good drug development practice and provides better health information
390 for both genders across demographic groups.[9]

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[4] The 1993 ICH guideline is available at 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).

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

[6] Ibid.

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

[8] 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.

[9] 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

391
392 • In 2016, Section 2041[10] of the 21st Century Cures Act,[11] required the establishment
393 of a Task Force on Research Specific to Pregnant Women and Lactating Women.
394 The task force was charged with providing advice and guidance to the Secretary of
395 Health and Human Services on Federal activities related to identifying and addressing
396 gaps in knowledge and research regarding safe and effective therapies for pregnant
397 women and lactating women.[12] The task force convened from August 2017 to May
398 2018 and developed recommendations to address areas such as building research
399 infrastructure and networks and overcoming participation barriers for pregnant
400 women and lactating women.[13]
401
402 • In April 2018, FDA published a draft guidance for industry on scientific and ethical
403 considerations for inclusion of pregnant women in clinical trials.[14]
404
405 • In May 2019, FDA issued two draft guidances providing trial design
406 recommendations for postapproval pregnancy safety studies[15] and for clinical
407 lactation studies.[16]

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

[10] 42 U.S.C. 289a-2, 130 Stat. 1033, 1070.

[11] 130 Stat. 1033, Pub. L. 114-255 (Jan. 6, 2016).

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

[13] *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.

[14] *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.

[15] *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.

[16] *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.

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.[1]
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.[2]
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.[3]
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."[4]
429
430 • The website 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.[5]
433

[1] "Inside Clinical Trials: Testing Medical Products in People," available at https://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm.

[2] "Minorities in Clinical Trials," available at https://www.fda.gov/ForConsumers/ByAudience/MinorityHealth/ucm472295.htm.

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

[4] "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.

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

434 • ResearchMatch, a public clinical research registry partially funded by NIH's National
435 Center for Advancing Translational Sciences, connects researchers with people who
436 are interested in participating in clinical trials.[6]

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