Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

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Clinical/Medical
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Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to sponsors developing medical products² on the approach for developing a Race and Ethnicity Diversity Plan (henceforth referred to as the “Plan”) to enroll representative numbers of participants from underrepresented racial and ethnic populations in the United States, such as Black or African American, Hispanic/Latino, Indigenous and Native American, Asian, Native Hawaiian and Other Pacific Islanders, and other persons of color, in clinical trials.³ Individuals from these populations are frequently underrepresented in biomedical research despite having a disproportionate disease burden for certain diseases relative to their proportional representation in the general population. Adequate representation of these populations in clinical trials and studies supporting regulatory submissions helps ensure that the data generated in the development program reflect the racial and ethnic diversity of the population expected to use the medical product if approved, and may

¹ This guidance has been prepared by the Oncology Center of Excellence (OCE) in collaboration with the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Office of Minority Health and Health Equity (OMHHE) at the Food and Drug Administration.

² For the purposes of this guidance, medical product is used to refer to human drugs (including human biological products that are regulated as drugs) and medical devices.

³ FDA follows the Office of Management and Budget’s definitions of race and ethnicity. See Office of Management and Budget (OMB) Directive No. 15 Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity (October 30, 1997), available at https://www.whitehouse.gov/wp-content/uploads/2017/11/Revisions-to-the-Standards-for-the-Classification-of-Federal-Data-on-Race-and-Ethnicity-October30-1997.pdf. Consistent with OMB Policy Directive 15, the categories in this classification are social-political constructs and should not be interpreted as being scientific or anthropological in nature. Ethnicity is comprised of two categories: Hispanic/Latino or not Hispanic/Latino. Race is comprised of five minimum categories: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. In certain situations, as recommended in OMB Policy Directive 15, more detailed race and ethnicity information may be desired. OMB standards do not designate underrepresented populations, thus FDA’s recommendations regarding race and ethnicity data in clinical trials provide additional guidance, 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/regulatory-information/search-fda-guidance-documents.
potentially identify effects on safety or efficacy outcomes that may be associated with, or occur more frequently within these populations.

As discussed below, this guidance focuses specifically on racial and ethnic demographic characteristics of study populations, recognizing the broader issues regarding health disparities and differential access to health care in certain racial and ethnic populations, many of whom are part of underserved communities. However, FDA advises sponsors to seek diversity in clinical trial enrollment beyond populations defined by race and ethnicity, including other underrepresented populations defined by demographics such as sex, gender identity\(^4\), age, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity. FDA encourages sponsors to also submit plans that help ensure the adequate participation of relevant and underrepresented populations and analyses of data collected from clinically relevant subpopulations.\(^5\)

This guidance expands on FDA’s guidance, *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016), which outlines how to collect and present race and ethnicity data in submissions to the FDA and recommends that sponsors develop and submit a plan to address inclusion of clinically relevant populations, for discussion to the Agency. Given the importance of increasing enrollment from historically underrepresented racial and ethnic populations, FDA is publishing this guidance to provide detail on what sponsors should include in a Race and Ethnicity Diversity Plan. As described in further detail below, FDA recommends that a Plan to enroll representative numbers of participants from historically underrepresented racial and ethnic populations be submitted to the investigational new drug (IND) application, for a drug, including biological products regulated as drugs, or the investigational device exemption (IDE) application, for a device. This Plan should be discussed with the FDA as soon as practicable during medical product development. For drugs, this should occur no later than when a sponsor is seeking feedback regarding the applicable pivotal trial(s) for the drug (often during the End of Phase 2 (EOP2) meeting). The current guidance provides general considerations for the content and format of the Plan. This guidance is not intended to address all issues related to the clinical development of medical products such as the design of studies, trial endpoints, or the data package necessary to support a marketing application; sponsors should refer to the appropriate FDA guidance documents for FDA recommendations on these matters.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is


\(^5\) Adequate participation and analyses of data collected from clinically relevant subpopulations may provide important information pertaining to medical product safety and effectiveness for product labeling. Additional patient characteristics such as age, sex, gender, geographic location (e.g., rural), emotional, physical, sensory, and cognitive capabilities can often be important variables when evaluating medical product safety and efficacy. While these additional characteristics are not addressed in this guidance, FDA encourages sponsors to consider broadening their diversity plans to include all clinically relevant populations as appropriate. FDA guidance on *Enhancing the Diversity of Clinical Trial Populations: Eligibility Criteria, Enrollment Practices, and Trial Designs* encourages the inclusion of persons with disabilities in clinical trials including during the study design phase. For example, FDA guidance recommends that sponsors consider the recruitment challenges that may occur because of the planned visit schedule and difficulties with accessibility. FDA also has guidance on inclusion of older adults in clinical trials.
intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Clinical trials are used to characterize the safety and effectiveness of medical products intended for the prevention, treatment, or diagnosis of many diseases, including those that are serious and life-threatening. Across many therapeutic areas, participation in clinical trials may be an important component of a participant’s clinical care.

FDA regulations require IND holders to include in their annual reports, among other things, the total number of subjects initially planned for inclusion in a clinical study and the number entered into the study to date, tabulated by age group, race, and gender. In addition, a new drug application (NDA) must present effectiveness and safety data by gender, age, and race and must identify any modifications of dose or dose interval needed for a specific subgroup.

Medical product development programs should consider the clinical and demographic factors that impact the generalizability of study results with respect to the patient population that will use the medical product once it is approved. Diverse populations as defined by race and ethnicity are relevant to the evaluation of medical products and there have been some observed correlations between self-reported race, ancestry, genetic variations or ethnicity, and response. FDA has issued several sets of recommendations to improve clinical trial diversity. These recommendations address a range of topics, including: the collection and analysis of racial and ethnic data; measures that enhance diversity in clinical trials; and the broadening of eligibility criteria when scientifically appropriate to improve clinical trial participation. Stakeholders have also recommended that sponsors develop a plan that outlines the operational measures that will be implemented to ensure diverse clinical trial participation to improve the generation of evidence regarding safety and effectiveness across the entire population. Such measures could include but are not limited to offering financial reimbursement for expenses incurred by

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6 See 21 CFR 312.33(a)(2).
7 See 21 CFR 314.50(d)(5)(v and vi).
10 See the following three guidances for industry: Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs (November 2020); Collection of Race and Ethnicity Data in Clinical Trials (October 2016); and Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies (September 2017).
participation in a clinical trial or study (e.g., travel or lodging)\textsuperscript{12}, providing language access to participants with limited English language proficiency, and partnering with community-based organizations to provide support to study or trial participants. FDA guidance documents define a diverse population, when applicable, to be inclusive of all populations as defined by demographic factors such as race, ethnicity, sex, gender identity, age, pregnancy status, lactation status\textsuperscript{13}, and by the presence of certain clinical characteristics such as multiple comorbidities.

Some individuals from these groups have often been underrepresented in medical product development and FDA considers their representation in clinical trials and studies to be a priority. FDA has, for some of these populations, already published specific guidance (e.g., enrollment of women, including pregnant and lactating women, and older adults).\textsuperscript{14,15} However, FDA is focusing this guidance on diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations because the lack of representation of these populations in clinical research reflects, in part, a broader issue regarding differential access to health care\textsuperscript{16}, including access to centers that conduct clinical research programs for new therapies and awareness of clinical trials conducted there. In addition, mistrust of the clinical research system may stem from historical events that adversely impacted racial and ethnic minorities, such as the unethical Tuskegee experiments.\textsuperscript{17} Clinical trials designed to include pediatric participants should also take into account adequate representation of children from racial and ethnic minority backgrounds.\textsuperscript{18}

Swift development and approval of medical products is a highly desirable goal for the public, sponsors, and the FDA. There has been increasing reliance on relatively small studies, intermediate endpoints, and innovative study designs to expedite development and approval of medical products. However, these methods can also lead to lower enrollment of underrepresented populations. FDA recognizes the importance of ensuring diversity in clinical trials and has provided specific guidance for certain populations, such as pregnant and lactating women, older adults, and individuals from racial and ethnic minority backgrounds. This guidance is designed to improve the representation of these populations in clinical research and to address historical mistrust that may have led to underrepresentation in the past. By focusing on diversity plans, FDA aims to ensure that all populations are adequately represented in clinical trials, reflecting the diversity of the general population and promoting access to health care opportunities.
medical products, notably for rare diseases and for serious and life-threatening conditions.

Specific approaches are needed to both obtain data in diverse populations and facilitate efficient medical product development and approval. This underscores the importance of prospectively defining the approach to generating data for a broader and more diverse population early in the development program. Consistent implementation of actions to improve racial and ethnic diversity in clinical trials and studies can support early access to medical discoveries and innovations, improve the generalizability of results across all patient populations, improve our understanding of the disease and/or medical product under study, and inform the safe and effective use of the medical product for all patients who are expected to use the medical product if approved.

III. WHEN A RACE AND ETHNICITY DIVERSITY PLAN IS RECOMMENDED

FDA recommends a Plan be submitted for medical products for which an IND submission is required and/or for which clinical studies are intended to support a marketing submission under section 351(a) of the Public Health Service Act for a standalone Biologics License Application (BLA), or under 505(b)(1) or 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) for an NDA. A Plan is also recommended for medical products for which an IDE is required and/or for which clinical studies are intended to support a device marketing submission, whether a premarket notification (510(k)), premarket approval (PMA) application, a De Novo classification request, or a humanitarian device exemption (HDE) application. FDA will evaluate the Race and Ethnicity Diversity Plan as an important part of the sponsor’s development program.

IV. TIMELINES AND PROCESS FOR SUBMITTING RACE AND ETHNICITY DIVERSITY PLANS

Sponsors may discuss their strategy to enroll a diverse study population at any time throughout the medical product’s development.24

A. For drugs, sponsors should submit the Plan to the relevant IND application as soon as practicable during drug development but no later than when a sponsor is seeking feedback regarding the applicable pivotal trial(s) for the drug (often at the EOP2 meeting). The Plan can be submitted to the IND as part of a milestone meeting package,

19 To the extent that the submission will include clinical studies that are sponsored by the applicant.
20 See 21 CFR 807
21 See 21 CFR 814.20
22 See section 513(f)(2) of the FD&C Act
23 See 21 CFR 814.104
24 The plan should emphasize the enrollment of participants from underrepresented racial and ethnic populations early and throughout medical product development to ensure the availability of sufficient data about the safety and effectiveness of the product in diverse populations. In the event that recruitment goals are not met despite best efforts, sponsors should discuss with FDA a plan to collect this data in the post-marketing setting.
or on its own. Sponsors should request FDA feedback on the Plan by including specific questions in a formal milestone meeting request and Meeting Package.\textsuperscript{25}

B. For devices, sponsors should submit their Plan as part of the investigational plan included in the IDE application. To discuss a proposed enrollment strategy before submitting the Plan to the IDE or for clinical studies not conducted under an IDE, a sponsor should follow the Q-submission process for obtaining feedback or requesting a meeting with FDA.

C. For IND, IDE, or Q submissions containing a Plan, sponsors should alert the FDA by marking the submission with “\textbf{RACE AND ETHNICITY DIVERSITY PLAN}” in large, bolded type in the cover letter. FDA may request that sponsors provide periodic updates to specific components of the Plan throughout medical product development.

D. Sponsors should include the Plan in the marketing application for the medical product as well as a description of the successes and challenges in implementing it.

V. \textbf{CONTENT OF THE RACE AND ETHNICITY DIVERSITY PLAN (THE PLAN)}

- Sponsors should define enrollment goals for underrepresented racial and ethnic participants as early as practicable in clinical development for a given indication. These enrollment goals should be based in part on the pre-specified protocol objectives of the investigation. While in many cases race- and/or ethnicity-defined populations may be genetically heterogenous such that analyses to characterize differential effects due to pharmacogenomic variability may be difficult to discern, the Plan should begin with an assessment of any data that may indicate the potential for a medical product to have differential safety or effectiveness associated with race or ethnicity. For drug development, as applicable to the particular drug, the collection of sufficient pharmacokinetic (PK), pharmacodynamic (PD), and pharmacogenomic data from a diverse population is strongly encouraged to inform analyses of drug exposure and response.\textsuperscript{26} For devices, data on the relevant factors for device performance (e.g., phenotypic, anatomical, or biological) should be collected to inform any differential effects across a diverse population. For example, variations in skin pigmentation exist across diverse populations and it is known that skin pigmentation can affect the performance of certain devices. For studies of such devices (e.g., pulse oximeters), skin pigmentation data in a diverse population would be a relevant attribute to collect to inform the assessment of any differential effects.

\textsuperscript{25} See draft guidance for industry \textit{Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products} (December 2017). When final, this guidance will represent the FDA’s current thinking on this topic.

\textsuperscript{26} See guidance for industry \textit{Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications} (May 2003) and draft guidance for industry \textit{Population Pharmacokinetics} (July 2019). When final, this guidance will represent the FDA’s current thinking on this topic.
The Plan should describe the planned assessment of race and ethnicity in addition to other covariates with known potential to affect the safety and effectiveness of the medical product. In particular, for drugs, covariates with known potential to affect PK and PD should be assessed in order to facilitate exposure-response analyses and to inform safe and effective dosing regimens across the intended patient population, as applicable. For devices, device performance may be impacted by factors associated with race (e.g., the ability of a device to detect skin cancer based on skin pigmentation).

When there are data that indicate that the medical product may perform differentially across the population based on factors associated with race or ethnicity, the Plan should specify the study design features that will support analyses that will inform the safety and effectiveness of the medical product in the relevant racial and ethnic populations. In some cases, increased (i.e., greater than proportional) enrollment of certain populations may be needed to elucidate potential important differences. When there are no data that indicate that race or ethnicity will impact safety or effectiveness, it is nonetheless appropriate that enrollment reflects the epidemiology of the disease. FDA recognizes that enrollment based on epidemiology alone may not be sufficient to detect any differences in safety and effectiveness or make such inferences; however, consistent representative enrollment may provide opportunities for pooling data to evaluate outcomes by race and ethnicity.

The Plan should outline the sponsor’s plan to collect data to explore the potential for differences in safety and/or effectiveness associated with race and ethnicity throughout the entire development life-cycle of the medical product and not just during the pivotal trial(s) or studies.

In certain situations, it may be challenging to set an enrollment goal based on the epidemiology of the disease due to limited data to characterize the incidence and/or prevalence of the disease across diverse racial/ethnic populations (e.g., diseases that are defined by the presence of a rare molecular aberration). FDA encourages sponsors to leverage various data sources (e.g., published literature and real-world data) to set enrollment goals; if this is not feasible, it may be appropriate to set the enrollment goal based on demographics in the overall population with the disease or condition.

The Plan should include the clinical pediatric studies that are planned for inclusion as part of the pediatric development of the medical product.

The table below outlines the recommended elements of the Plan. Note that the examples provided in the table are intended to illustrate the type of information that should be included in the Plan and are not meant to be an exhaustive list of the measures that may be undertaken to improve diversity in clinical trials or studies.

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommended Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overview of the disease/condition</td>
<td>A. Describe available data on the pathophysiology of the disease or condition in underrepresented racial and ethnic populations. As appropriate, describe</td>
</tr>
</tbody>
</table>
### Contains Nonbinding Recommendations

*Draft — Not for Implementation*

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommended Scope</th>
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<tbody>
<tr>
<td>any differential application or use of currently available prevention, screening or diagnostic strategies and treatments, across racial and ethnic populations.</td>
<td></td>
</tr>
<tr>
<td>B. Discuss the current understanding of and available evidence supporting any similarities and/or differences in the disease or condition under study that are associated with the underrepresented racial and ethnic populations in the United States.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Scope of medical product development program</th>
<th>Briefly describe the planned trials or studies that will support the medical product’s safety, effectiveness and, if a drug, dosage in a future marketing submission. Outline the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Study design, study population (including study eligibility criteria), endpoints and, the expected geographic locations of the trials or studies and how these aspects of the trial or study may specifically address inclusion of underrepresented racial and ethnic populations.</td>
<td></td>
</tr>
<tr>
<td>B. As applicable, summarize any differential findings from clinical pharmacology studies (PK/PD data, pharmacogenomics) that may be associated with certain racial and ethnic populations and/or other relevant information.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Goals for enrollment of underrepresented racial and ethnic participants</th>
<th>Define and provide justification for the planned enrollment of participants from underrepresented racial and ethnic populations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Specify underrepresented racial and ethnic populations based on assessment in Category #1.</td>
<td></td>
</tr>
<tr>
<td>B. Specify goals for enrollment of underrepresented racial and ethnic participants (e.g., based on the epidemiology of the disease and/or based on <em>a priori</em> information that may impact outcomes across racial and ethnic groups; and where appropriate, leverage pooled data sources or use demographic data in general population). In some cases, increased (i.e., greater than proportional) enrollment of certain populations may be needed to elucidate potential important differences.</td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Category</th>
<th>Recommended Scope</th>
</tr>
</thead>
</table>
| 4. Specific plan of action to enroll and retain diverse participants | A. Describe in detail the operational measures that will be implemented to enroll and retain underrepresented racial and ethnic participants in the planned trial(s) or studies, and the planned use of data to characterize safety, efficacy, and optimal dosage in these participants, when applicable.  
   
   B. Describe specific trial enrollment and retention strategies, including but not limited to:  
      i. site location and access (e.g., language assistance for persons with limited English proficiency, reasonable modifications for persons with disabilities, and other issues such as transportation);  
      ii. sustained community engagement (e.g., community advisory boards and navigators, community health workers, patient advocacy groups, local healthcare providers, etc.);  
      iii. reducing burdens due to trial/study design/conduct (e.g., number/frequency of study-related procedures, use of local laboratory/imaging, telehealth);  
   
   C. Describe metrics to ensure that diverse participant enrollment goals are achieved and specify actions to be implemented during the conduct of the trial(s) or studies if planned enrollment goals are not met. |
| 5. Status of meeting enrollment goals (as applicable) | A. As the diversity plan is updated (when applicable), discuss the status of meeting enrollment goals. If the sponsor is not able to achieve enrollment goals despite best efforts, discuss a plan and justification for collecting data in the post-marketing setting. |