June 12, 2022

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2021-D-0789: Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance on **Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials.**

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO has two key overarching recommendations to improve this draft guidance and enrollment of participants from underrepresented racial and ethnic populations in clinical trials:

1. Patient and Community Engagement/Building Trust:

BIO recognizes that community engagement and building trust are essential aspects of improving enrollment of participants from underrepresented racial and ethnic populations in clinical trials. It will be important during FDA-sponsor communication and engagement to ensure that FDA has expertise in actions that will promote community engagement and trust to provide useful feedback to sponsors to address enrollment and retention challenges. BIO proposes that the Agency ensures that they have the necessary expertise to be able to address concerns related to enrolling and retaining diverse patients (i.e., site operations, community engagement strategies and reducing burdens to trial/study design and conduct).

BIO acknowledges the importance of clinical care and encourages the Agency to also make recommendations in this draft guidance for diversity among clinical trial investigators and the broader research team. Increased diversity of clinical trial investigators and site staff will increase trust as diverse participants are known to have more favorable interactions when the patient-physician racial and ethnic background is concordant. The National Medical Association (NMA) uses a statistic that only 1% of clinical investigators are Black. BIO strongly encourages the Agency to engage with sponsors and other stakeholders to better understand and address these challenges that continue to impact the diversity of clinical trials.

2. FDA-Sponsor Communication and Engagement

BIO proposes that the Agency work with sponsors to ensure that FDA-sponsor communications are streamlined and consistently implemented across the Agency, building from provisions described in the PDUFA VII Commitment Letter. Specifically, it would be helpful to provide more clarity on the timing and operational aspects of FDA's expected review of the Diversity Plan, including submitted updates to the Diversity Plan, to ensure that sponsors and FDA have robust and productive communications. We recommend that the Agency consider including such recommendations as part of revisions to the Best Practices for Communication Between IND Sponsors and FDA During Drug Development guidance that will be updated during PDUFA VII.

General Comments

Focus of Draft Guidance

BIO appreciates that the Agency is focusing on race and ethnicity in this draft guidance and recommends consolidating references to other demographic groups to the introduction to ensure that the scope of the guidance is clear. Since this draft guidance has many new concepts, it may be helpful for the Agency to consider appending a formal reference section to the draft guidance.

BIO strongly recommends that the Agency cross-reference existing guidance such as, "Collection of Race and Ethnicity Data in Clinical Trials" and "Enhancing the Diversity of Clinical Trial Populations: Eligibility Criteria, Enrollment Practices, and Trial Designs" to highlight the Agency's approach to individuals that identify as more than one race/ethnicity and other considerations. Given the emphasis on socio-cultural issues contributing to under-representation of certain racial and ethnic groups it would be appropriate to acknowledge the importance of collecting and analyzing data by "self-assigned" or "self-reported" race and ethnicity.

BIO also recommends that the Agency provide more clarity on:

- the recommended course of action when a particular disease or condition is not prevalent in a given ethnic population or race and/or when enrollment is a challenge due to the disease context, e.g., rare diseases and other therapeutic areas;
- how to capture multiple study level goals within one diversity plan if the IND and/or NDA encapsulates several clinical trials;
- how to address missing racial/ethnic data, specifically when patients choose not to identify their race and/or ethnicity; and
- how to present final data and assess achievement of diversity goals.

Timing of Submitting Diversity Plans

BIO appreciates the Agency encouraging sponsors to submit the Plan as soon as practical but no later than when a sponsor is seeking feedback regarding the applicable pivotal trial(s) for the drug; i.e., no later than the End of Phase 2 meeting. BIO recommends that the Agency consider clarifying expectations for what should be submitted at various stages of development and when and/or how to update the Plan as more information becomes available. Specifically,

mechanisms for submission and review of the Diversity Plan and procedural considerations should be clarified in the draft guidance, such as:

- FDA expected review duration of the Diversity Plan
- Preferred location of the Diversity Plan within the Dossier
- Guidance on if/when the Diversity Plan can be revised

Enrollment – US and Global Considerations

Clinical development programs are often conducted globally, which adds a level of complexity to understanding the epidemiology of the disease. BIO recommends that the Agency consider these complexities and provide more clarity on how data collected globally could be used. BIO recommends that the Agency provide guidance as to how ICH E5 Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data could enable the use of global clinical trials when the intrinsic and extrinsic factors support the ability to use those data. BIO also recommends that the Agency provide guidance on how the ICH E17 Guideline on General Principles for Planning and Design of Multi-Regional Clinical Trials should be considered. There may be other factors that impact enrollment and it will be important for FDA to be flexible and provide guidance to sponsors on how to address these challenges effectively. Hence, BIO strongly recommends that the Agency consider convening public meetings with industry and other stakeholders to discuss best practices to recruit, enroll and retain diverse patient populations in the context of global development programs.

Data Reporting

BIO supports efforts to improve clinical trial diversity and emphasizes that the Agency is in a unique role to provide aggregate reporting of goals set and missed and/or methods and approaches used by sponsors to include diverse populations. This information will be extremely helpful to all stakeholders to ensure that we are making progress on our commitment to improving clinical trial diversity. It would also be helpful for the Agency to consider how this information will complement and/or be incorporated into Drug Trials Snapshots.

Conclusion

BIO appreciates the opportunity to submit comments regarding guidance on this critical topic. Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments as needed, and we look forward to future opportunities to collaborate with the Agency on efforts to improve and support clinical trial diversity.

Sincerely,

/s/
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/s/
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/s/
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SPECIFIC COMMENTS

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I. INTRODUCTION		
Lines 19-21	The Draft Guidance states: "…developing a Race and Ethnicity Diversity Plan…to enroll representative numbers of participants …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." "…and other persons of color": can be considered negative categorization. We suggest revising as indicated. It is unclear which underrepresented populations FDA expects to see included in the Plan.	BIO recommends the following edit: "…and other **underrepresented or underserved populations**." BIO also recommends that the Agency provide additional guidance on how sponsors should determine populations for inclusion in the Plan and if FDA expects written justifications for populations not included would be beneficial.
Lines 33-36	The draft guidance states: "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, age, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity." This statement broadens the scope of the guidance well beyond underrepresented racial and ethnic populations. We believe that other underrepresented populations (eg, those defined by pregnancy or lactation status,	BIO supports the need for additional factors to be considered and studied and efforts should be made to increase clinical trial diversity on a multitude of levels, however we believe the Plans should be focused on racial and ethnic demographic populations, as should this guidance.

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	among others), with complex benefit-risk considerations are best reserved for separate FDA guidance that focuses on those populations. This comment also applies to the sentence beginning on line 97 in the guidance. Socioeconomic status (social determinants of health) may not be directly captured in source documentation, and/or inclusion/exclusion criteria are not written in a way to include/exclude based on their current socioeconomic status. This is the only location within the document that references socioeconomic status.	
Lines 47-54	One IND and/or NDA may encapsulate several clinical trials	BIO recommends the Agency provide clarity on how to capture multiple study level goals within one diversity plan.
Lines 51-54	Line 51 of the Draft Guidance states: "This Plan should be discussed with the FDA as soon as practicable…" Line 149 of the Draft Guidance states: "…sponsors should submit the Plan to the relevant IND application…" While this timing may seem reasonable in lines 207 – 211, the agency seems to suggest a broader scope of studies beyond the pivotal trial(s). "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	BIO recommends the following edit for clarity and consistency: "This Plan should be **submitted to the application and** discussed with the FDA…" It may also be helpful to cross-reference Section IV. At a minimum, the Plan should focus and address data collection for pivotal studies. Sponsors may outline in the Plan other studies where data could be collected for registration in accordance with the Plan, but the metrics and goals should reflect the pivotal program. Additionally, BIO recommends that the Agency provide clarification to the term "as soon as practicable".

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	throughout t**he entire development life-cycle** of the medical product and not just during the pivotal trial(s) or studies." While it is important for sponsors to try to collect data from as much clinical experience with the drug, in consideration that the Plan requires developing executable steps to try to increase the underrepresented populations, this statement may be suggesting development of a plan and discussion prior to the EOP2 meeting if data from early development life cycle is desired by agency. Additionally, on accelerated pathway submissions, the number of studies may be limited.	
Lines 55-58	Original guidance text: "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." Consistent with our recommendation above on lines 33-36, we recommend noting that other special populations are not addressed in this guidance.	BIO recommends the following changes: "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, enrollment of special populations such as pregnant or lactating women, 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."
II. BACKGROUND		
Lines 90-93	The Draft Guidance states:	BIO recommends the following edit:

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	"Stakeholders have 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." Implementation of operational measures are intended to enable and improve diverse clinical trial participation, but the outcome is often unpredictable and impact can only be determined once implemented.	"Stakeholders have recommended that sponsors develop a plan that outlines the operational measures that will be implemented to ~~ensure~~ **enable** diverse clinical trial participation…"
Lines 90 - 93	FDA should explicitly discuss how sponsors should consider race and ethinicity when submissions include MRCTs, i.e., patient self-reporting of "hispanic" does not apply to Spain, Portugal, etc.	BIO recommends that the Agency provide guidance as to how ICH E5 Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data could enable the use of global clinical trials when the intrinsic and extrinsic factors support the ability to use those data. BIO also recommends that the Agency provide guidance on how the ICH E17 Guideline on General Principles for Planning and Design of Multi-Regional Clinical Trials should be considered.
Lines 93-95	The Draft Guidance states: "Such measures could include but are not limited to offering financial reimbursement for expenses incurred by participation in a clinical study…." FDA should provide more description here on the barriers to participation.	BIO recommends that the Agency emphasize the guidance cited in footnote 10 and/or consider adding language considering that barriers to participation are not just financial. Other barriers may be related to time constraints, etc. The section could address reducing financial/time barriers to participation (e.g., remote visits, flexible scheduling, mobile nursing, digital health technology, etc.).

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Lines 96-97	The Draft Guidance states: "….and partnering with community-based organizations to provide support to study or trial participants." FDA should provide examples of community-based organizations.	"and partnering with **organizations (local health and advocacy groups, national groups, churches, other)** to support study trial participants"
Lines 97-100	The Draft Guidance states: "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, and by the presence of certain clinical characteristics such as multiple comorbidities." It is not clear which guidance documents are being referred to in this statement.	BIO supports the need for additional factors to be considered and studied and efforts should be made to increase clinical trial diversity on a multitude of levels, however we believe the Plans should be focused on racial and ethnic demographic populations, as should this guidance. BIO strongly recommends that the Agency cross-reference existing guidance such as, "Collection of Race and Ethnicity Data in Clinical Trials".
III. WHEN A RACE AND ETHNICITY DIVERSITY PLAN IS RECOMMENDED		
Line 132-136	The draft guidance states: "FDA recommends a Plan be submitted for medical products for which an IND submission is required and/or for which clinical studies…" There are situations where a unique IND is filed, but racial and ethnicity enrollment goals may not be necessary or feasible. For example, new oral dosage forms have distinct INDs, but we believe that a diversity plan should not be required in this instance.	BIO recommends that FDA provide additional guidance on how sponsors should proceed if diversity plans under the IND are not considered necessary or believe regulatory flexibility should be applied\
IV. TIMELINES AND PROCESS FOR SUBMITTING RACE AND ETHNICITY DIVERSITY PLANS		
Citation 24	The guidance states:	The citation should be moved to the body of the guidance and should address considerations for rare diseases drug

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	"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." This may cause a disproportionate amount of work for rare disease drug developers.	development programs.
Lines 153-154	The draft guidance states: "Sponsors should request FDA feedback on the Plan by including specific questions in a formal milestone meeting request and Meeting Package" Sponsors have received recent feedback from FDA limiting Sponsors to a total of 10 questions in an FDA meeting.	BIO recommends that in lieu of an FDA-Sponsor meeting, the Sponsor can submit a Race & Ethnicity Diversity Plan to FDA for written feedback. BIO further requests that FDA clarify that there are no limits on the number of questions that can be posed in an FDA meeting or exempt any questions relating to Race & Ethnicity Diversity Plans from the total number of questions. BIO also recommends that the Agency clarify whether sponsors can seek feedback about the diversity plan outside of milestone meeting requests and meeting packages.
Line 162	The draft guidance states: "*FDA may request that sponsors provide periodic updates to specific components of the Plan throughout medical product development*" Clarification may be needed on whether FDA is asking for an update on how the plan is going, or that FDA	BIO recommends the Agency clarify expectations around sponsors providing updates to the Agency. BIO recommends that the Agency clarify if they are asking for an update on how the plan is going or that the Agency could request that the sponsor update (i.e., change) the plan. BIO also recommends that the Agency consider providing sponsors with advanced notice of requested update. Finally, if FDA requests an update they should provide feedback to the sponsor on the update provided. BIO requests that the Agency consider providing a

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	could request that the sponsor update (i.e., change) the plan?	specific timeframe in which they will provide feedback to the sponsor. The timeliness of the feedback is important so that the sponsor has time to take FDA feedback into consideration.
Line 160-162	The draft guidance states: "For IND, IDE, or Q submissions containing a Plan, sponsors should alert the FDA by marking the submission with "RACE AND ETHNICITY DIVERSITY PLAN" in large, bolded type in the cover letter"	BIO requests that the Agency provide clarity on the location of the diversity plan within the dossier.
V. CONTENT OF THE RACE AND ETHNICITY DIVERSITY PLAN		
Lines 172-174	The Draft Guidance states: "These enrollment goals should be based in part on the pre-specified protocol objectives of the investigation." Consider an example to clarify what is being said here. It is not clear how enrollment goals should be based in part on protocol objectives.	BIO recommends that the Agency provide an example to clarify how enrollment goals should be based in part on pre-specified protocol objectives of the investigation.
Lines 174-178	The draft guidance states: "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." In rare disease trials, it may be challenging to assess data that indicate the potential for a medical product	BIO recommends that the Agency provide more clarity on how to address instances with limited data.

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	to have differential safety or effectiveness associated with race or ethnicity. It would be helpful for the Agency to provide more clarity on how to address instances with limited data.	
Lines 176-178	The draft guidance states: "…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."	BIO recommends that the Agency provides guidance on how to account for, for example, intra-ethnic racial differences among Latinos or among African American and Blacks from the Caribbean.
Lines 196-197	The draft guidance states: "When there are data that indicate that the medical product may perform differentially across the population …"	BIO recommends the following edit: "When there are data that indicate that the medical product may perform differentially **and/or disease and/or condition may present differently across** the population …"
Lines 200-201	The draft guidance states: "In some cases, increased (i.e., greater than proportional) enrollment of certain populations may be needed to elucidate potential important differences." This text implies studies will need to be powered to show a difference in these populations.	BIO recommends the Agency clarify this statement.
Lines 201-203	The draft guidance states: "When there are no data that indicate that race or ethnicity will impact safety or effectiveness, it is	BIO recommends that the Agency provide more clarity around expectations for establishing enrollment goals that reflect the epidemiology of the disease in the context of global clinical trials. BIO also recommends that the Agency convene sponsors and other stakeholders to further discuss

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	nonetheless appropriate that enrollment reflects the epidemiology of the disease" Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems. BIO firmly believes in the importance of studying the epidemiology of the disease and recognizes the limitation of existing data and diverse perspectives regarding epidemiology of the disease vs. demographics.	opportunities to improve existing epidemiological data sources and ensure a clear understanding on the epidemiology of the disease and the demographics of the population who are affected with the disease.
Lines 208-211	The draft guidance states: "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." While BIO agrees that it is important to explore potential differences in safety and/or effectiveness associated with race and ethnicity, the size of a Phase 2 program is often not large enough to detect such subtle differences.	BIO recommends that the Plan focus on pivotal studies to strike the appropriate balance between rapid drug development and assessment of safety and/or effectiveness associated with race and ethnicity. BIO recommends that the Agency clarify the meaning of "development life-cycle," i.e., IND to NDA. For Race & Ethnicity Diversity Plans submitted at End-of-Phase 2, it should be clarified that the submitted plan should be prospective in nature and/or reflect the totality of the clinical program. A retrospective plan to discuss individual trials that are already completed or substantially complete should not be required.
Lines 212-218	Line 212 indicates the paragraph is referring to the situation in which enrolment goals cannot be set based on race and ethnicity data due to limited epidemiology	BIO recommends clarifying which demographic characteristics of the disease population are being referred to in Line 218 when race and ethnicity data are not available.

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	data for the disease. Line 218 states that in this circumstance the enrollment goals be based on the demographics of the population with the disease.	BIO also suggests reiterating this language at the beginning of the guidance.
Lines 215-218	The Draft Guidance states: "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." This sentence is not clear. Presumably, this step would also requires accessing sources such as the literature or real-world data as the prior statement suggests. It would also be helpful to specify a suggested source for data on demographics such as U.S. Census data and/or other data sources. Please see comments for lines 201-203.	BIO recommends the Agency clarify how literature and/or real-world data may be used to set enrollment goals. BIO recommends that the Agency provide more clarity around expectations for establishing enrollment goals that reflect the epidemiology of the disease in the context of global clinical trials. BIO also recommends that the Agency convene sponsors and other stakeholders to further discuss opportunities to improve existing epidemiological data sources and ensure a clear understanding on the epidemiology of the disease and the demographics of the population who are affected with the disease.
Lines 219 – 220	It is unclear why the 'Plan' includes a broad request for inclusion of clinical pediatric studies. If an IND is intended exclusively for the treatment of a pediatric population (i.e., the indication only exists in a pediatric population), then the 'Plan' would already address this information. If an IND is within scope of the required pediatric study plan (PSP) submissions under PREA, then this requested information will already be contained within the PSP which are agreed with the Division.	BIO recommends that the draft guidance should be explicit about the ability to cross-reference agreed pediatric commitments (or existing INDs) which include information, OR, FDA should discuss how this new requested information on historically underrepresented racial and ethnic populations could be more seamlessly incorporated into existing templated FDA documents for review. This will reduce unnecessary redundancy.
Line 219-220	The draft guidance states: "The Plan should include the clinical pediatric studies that are planned for inclusion as part of the pediatric development of the medical product."	BIO recommends deleting the bullet on lines 219-220 If the Plan includes pediatric studies, the Plan needs to be cross-referenced in the PSP. Any differences in goals and metrics for pediatrics need to be reflected in the Plan.

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	Since pediatric study plans already exist for development programs, we do not believe this information needs to be repeated in the diversity plan. BIO agrees that sponsors should endeavor to increase participation of underrepresented populations in pediatric clinical trials. However, the rationale outlined under lines 176-181 may not be reflective of pediatric patients due to physiology across the age range (neonates to adolescents). "*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*." Additionally, the commitments for pediatric studies are contained and tracked by the sponsor and the agency through the content of the Pediatric Study Plans and its amendments. In consideration that these studies are (in many cases) exceedingly difficult to enroll in, and the Plan includes metrics and goals, it is unclear what the impact is to the registration or for phase 4 post approval commitments of a pediatric indication when goals outlined in the Plan are not met.	Clarification is needed as to the impact of not meeting the Plan goals for pediatric studies.

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Table Category 2B	The text currently recommends to present only "differential findings", without acknowledging that data providing evidence of similarity is also informative	BIO recommends the Agency consider aligning this wording with Category 1B which uses the phrase "available evidence supporting any similarities and/or differences"
Table Category 3	Goals for enrollment of underrepresented racial and ethnic participants It is unclear if goals for enrollment are meant to be cumulative across a development program or within study.	BIO recommends that the Agency provide more clarity around expectations for establishing enrollment goals that reflect the epidemiology of the disease in the context of global clinical trials. BIO recommends that the Agency clarify if the goals for enrollment are meant to be cumulative across a development program or within a study. BIO also recommends that the Agency convene sponsors and other stakeholders to further discuss opportunities to improve existing epidemiological data sources and ensure a clear understanding on the epidemiology of the disease and the demographics of the population who are affected with the disease.
Table Category 3B	Category 3. Goals for enrollment of underrepresented racial and ethnic participants The Draft Guidance states (bullet 3.B.) "or use demographic data in general population." It is unclear what is meant by demographic data in general population. Is this meant to mean census data or data related to the disease/condition under study? Does this mean that in some instances, enrollment goals based solely on the general population will be acceptable? If so, under what circumstances?	BIO recommends that the Agency clarify what is meant by demographic data in the general population. Specifically, if it is meant to mean census data or data related to the disease/condition under study and under what circumstances would enrollment goals based solely on the general population be acceptable.
Table Category 4	Scope B and Scope C Clarification is needed.	BIO recommends that it should be clarified in Recommended Scope B that each of these enrollment & retention strategies may not be applicable for each trial. Therefore, BIO recommends changing "including but not limited to" to "which may include".

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		For "reducing burdens due to trial/study design/conduct (e.g., number/frequency of study-related procedures, use of local laboratory/imaging, telehealth", this suggests that FDA would permit reduced / modified enrollment criteria, and reduced testing. FDA should provide additional guidance on what specific elements they would recommend implementing to reduce burdens so these can be implemented across industry. For Scope C ("Describe metrics to ensure that 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."), FDA should clarify the mechanisms by which Sponsors and FDA should engage in order to discuss these metrics in ongoing trials. BIO recommends that the Agency clarify what is meant by the term 'metrics'. Submission of data in Annual Reports does not appear to be an appropriate mechanism for FDA engagement.
Table, Category 4A	Category 4 Section A – We note the only reference to dose optimization in the guidance is in the recommended elements of the Plan. We request FDA clarify their expectations for optimal dose considerations in diverse subjects.	BIO notes the only reference to dose optimization in the guidance is in the recommended elements of the Plan. BIO requests FDA clarify their expectations for optimal dose considerations in diverse subjects.
Table, Category 4A	The "category" is stated as relating to enrollment and retention, but the description under "A" relates to "planned use of data to characterize safety, efficacy, and optimal dose	BIO recommends the Agency consider to either expand the description of the "category" to include "analysis". Or add an additional category for discussing planned use of data / analyses.
Table, Category 4Biii	Study Participation Burden may not be well understood for Ph3 studies prior to EOP2 meetings	BIO recommends the Agency provide additional guidance on updating the Plan.

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Table, Category 4Biii	FDA recommends the use of "local laboratories" as an example to reduce burdens due to trial/study design/conduct. We note FDA's position is different in other guidance documents. For example, in the Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Produce guidance, FDA recommends against use of local sites. It would be helpful for FDA to provide further clarity on the use of "local laboratories" for the scope of this guidance.	BIO recommends that the Agency provide further guidance on the use of "local laboratories" for the scope of this guidance.
Table, Category 5	Elements of the Plan 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. It would be helpful to understand when and how FDA expects to discuss the final enrollment goal status.	BIO recommends that if this is a pre-NDA discussion, the timing should be defined as "prior to submission." If this is expected at submission, then refer to comments of Line 164-165, where a deliverable needs more clarity from the agency to the Sponsor.
Table, Category 5	Category 5. Status of meeting enrollment goals (as applicable) The Draft Guidance states "As the diversity plan is updated (when applicable), discuss the status of meeting enrollment goals." It is unclear under what circumstances a sponsor can/should update their Plan and if those updates would trigger need for additional discussion and agreement with FDA.	BIO recommends that the Agency clarify under what circumstances a sponsor can/should update their Plan and if those updates would trigger need for additional discussion and agreement with FDA.

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Table, Category 5	Category 5. Status of meeting enrollment goals The Draft Guidance states "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" Is it presumed that postmarket data will be necessary if goals are not met? There should be opportunity to provide justification for not meeting enrollment goals. What would trigger an update to the study plan? Are there any metrics/updates required to FDA during the study, for accountability? How will FDA ensure the plan is attained, and what will be the impact to submission? FDA should also acknowledge that real world evidence may be supportive to continue to collect data postmarket.	Suggested edit: "If the sponsor is not able to achieve enrollment goals despite best efforts, **discuss reasons for missing the goals and whether or not collecting data in the post-marketing setting is necessary to ensure the safe and effective use of the medical product across racial or ethnic groups**." BIO recommends that the Agency acknowledge that real world evidence may be supportive to continue to collect data in the post market setting. BIO also recommends that the Agency provide additional clarity on "best efforts" and "post-marketing data collection".