BRIGHAM HEALTH
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MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

July 30, 2019 Submitted electronically at www.regulations.gov

Norman E. Sharpless, MD
FDA Commissioner
c/o Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA- 2019-D-1264
"Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry."

Dear Commissioner Sharpless:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the Food and Drug Administration (FDA)'s " Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry," published June 2019.

The MRCT Center is a research and policy center that addresses the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. In addition, the Center is involved in several in-country engagements and has a long-standing commitment to training global regulators, investigators, and others. Over the last two years, the MRCT Center has convened a working group to address the challenge of diverse representation in drug development and in clinical research more generally. Diversity needs to be addressed in order to understand variability in safety and effectiveness of drugs, devices, and biologics in the populations most likely to need them. While the work group has been helpful in preparing the comments below, the responsibility for the content of this document rests with the leadership of the MRCT Center, not with the workgroup, nor with the institutions affiliated with the authors.[1]

The MRCT Center applauds the FDA's commitment to enhancing diversity by issuing this draft guidance, as well as the reference to FDA's prior documents and guidance on broadening eligibility criteria that are summarized in Appendix A. The additional considerations for relevant stakeholders to consider in their efforts to increase diversity are important practical recommendations. Specific and directed statements from the Agency will help stakeholders focus on the importance of increasing inclusion in enrollment, and the specific recommendations

[1] Brigham and Women's Hospital, Ropes and Gray LLP, Columbia University, Harvard Medical School and Harvard University.

presented here are helpful in this regard. We endorse FDA's draft guidance, and our comments below are intended to clarify, strengthen, and expand the recommendations of the Agency on this important problem.

Our specific comments below are divided into suggestions related to the scope and applicability of the draft guidance and specific comments and questions related to draft recommendations. We begin below with comments about the use and importance of the term "diversity" in the draft guidance.

A. Defining Diversity in Clinical Trials

1. In its draft guidance, the FDA defines the term *diversity* as inclusive of both demographic and non-demographic populations. It would be useful for the FDA to more clearly elucidate the scientific reasons for its focus on diversity: that is, to understand the biological variability in safety, efficacy, and perhaps patient experience and value across the populations likely to use the medical treatment. The scientific value of including diverse populations in clinical trials representing, by category, those affected by the condition of interest or the "at risk" population for the treatment under investigation, is to understand variability of effect. Within defined study populations, clinical trials will generate an expanded evidence base inclusive of those with laboratory, medical, physiological, and clinical characteristics for whom safety and outcome measures may differ. What defines appropriate inclusion, and what defines the categories themselves, requires study and will vary for each disease, subpopulation, treatment, and phase of development, based in part on epidemiology, genetics, physiology, and other factors. Categories include organ dysfunction, but also age, sex, gender, race, ethnicity, geography, ancestry, genetic differences, and social determinants of health (e.g. socioeconomic status). Each can be associated, directly or indirectly, with important differences in disease manifestation, drug metabolism, drug response, and adverse event profile. In this way, diversity in study inclusion focuses attention on a range of group-related variables, some directly biologically relevant, other mediators of latent biological processes that are currently unidentified. It will be helpful for the Agency to more clearly outline the scientific basis for the attention to diversity in clinical trials in this guidance, and why it is concordant with and fundamental to the mission of the FDA. Because there are important healthcare, social, and historical dimensions to diversity, we believe it would be helpful for the FDA to explain why these other dimensions are not addressed in this document or if they are beyond the scope and jurisdiction of the FDA.

2. While we believe that the focus of the FDA on diversity relates to the scientific dimensions of variation in efficacy and safety, the document does not reference or discuss the ethical basis of diverse inclusion in clinical research. We think that this is important, even if it is viewed as falling outside the mission of the FDA as legislated by Congress. The ethical underpinning for diverse representation rests, at least in part, on the idea that the risks and benefits of research should be equitably distributed across the population at risk for a particular condition. Arguably, concerns about exposure of subjects to research risk have led to overly restrictive eligibility criteria, for example, by excluding healthy

elderly patients, adolescents, and pregnant woman, among others. While risk exposure must of course be considered in research, risk avoidance must be carefully balanced with the goals of choice of inclusion criteria so as not to stall drug development for a broader population in need of novel therapies. In the absence of appropriate diverse representation, the result is that the product is marketed, widely distributed, and used by populations in an uncontrolled and untested manner, putting unstudied populations at uncertain risk and with uncertain benefit. Further, clinical trials can be an important patient care mechanism and should be intentionally designed for and made available to all potentially eligible patients. Participants excluded from clinical trials on investigational products cannot benefit from early access to novel, potentially beneficial therapies through clinical trials, access that is particularly important in the setting of unmet medical need.[2] Finally, there is a fundamental issue of fairness and justice that must be taken into account. Clinical development of drugs, devices, and biologics should serve the needs of those who are affected by the disease or condition. These ethical dimensions substantiate the motivation of the FDA and other responsible stakeholders to address the issue, and we think are important to embed in the document itself.

3. While diverse inclusion in clinical trials is an important goal, the expansion of enrollment to populations that may have not been studied previously may potentially put those individuals at increased risk, and certainly some risks will be unknown. Explicit mention of the need for a careful balancing of these risks with the benefit of inclusion should be addressed in the guidance.

4. While the title of the document addresses diversity, and the guidance appears to address "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)" (Guidance, footnote 4), almost all the examples given refer to eligibility criteria for non-demographic criteria (e.g. comorbidities, polypharmacy, organ dysfunction, etc.). The guidance cites the example of PK/PD differences in "the elderly and patients with liver or kidney dysfunction" (line 142); here one could include an example of PK/PD differences of other demographics and across subgroups. It would be important to include examples of exclusion criteria based on demographic criteria, and examples of broadening eligibility and recruitment strategies in these populations (other than age, which is referenced by example). For instance, the lower white cell count of some persons of African descent is a benign variant that nevertheless may cause individuals to be considered ineligible for a clinical trial. Of course, varying racial/ethnic and/or ancestral backgrounds may have relevance to

[2]Conversely, inclusion of participants in countries where there is no intention to seek regulatory approval or market access raises ethical concerns, especially if there are no provisions to provide product access to participants post-trial. Increasing barriers to reimbursement post-approval in some countries have served as deterrents for some sponsors to conduct clinical trials in those countries or regions.

biomarker strategies and other clinical trial design considerations in addition to eligibility parameters.

5. Further, we believe that additional subpopulations that may have traditionally been inappropriately excluded from clinical trials should be explicitly described: individuals whose primary language is not English, transgender individuals, individuals with disabilities, economically vulnerable participants, etc. Wherein these populations have been discussed in other FDA guidance, reference to those documents would be helpful.

6. Generally, transgender individuals are excluded from clinical trials as these individuals are usually on lifelong hormonal treatments. It would be helpful if the FDA would issue guidance specific to when transgender individuals may participate in clinical trials and any points to consider for their inclusion, to help sponsors understand that these individuals can and should be considered in clinical trial participant pools.

B. Scope and applicability

1. We believe this complex document would benefit from the addition of a guiding framework. The expansion of eligibility criteria appears to focus more on non-demographic criteria, while issues specific to race/ethnicity and sex/gender appear more central to the later section III. Framing the guidance more explicitly would demonstrate that considerations of many parameters for inclusion are essential to increase diversity of the participant population.

2. While we appreciate that the guidance was issued in part to satisfy the mandate under section 620(a)(3) of the FDA Reauthorization Act of 2017 (FDARA), we also believe that the guidance is responsive to the 21st Century Cures Act. We encourage FDA to reference the latter act as well.

3. We believe that the guidance applies equally to drugs, biological products, and devices. It is not clear why the guidance is limited to drugs alone (other than fulfillment of the FDARA mandate). We encourage FDA to expand the applicability of the guidance.

4. FDA accepts data from organizations and sites globally and, they may also manufacture their products abroad and wish to market their products in the USA. Many phase 3 and, increasingly, phase 2, programs are global. The Agency mentions the applicability of this guidance to sponsors intending to submit a new drug application or a biologics license application. However, it is not clear whether the Agency's recommendations have considered diversity within the context of US studies and submissions only, or also as it pertains to geographic diversity within the context of global clinical trials. We suggest FDA clarify the scope of the guidance as it pertains to global geographic diversity.

5. The document mentions that sponsors should consider geographic location of sites in order to improve demographic diversity of the trial population (line 245). To what extent should geographic location be assessed for site selection (e.g. urban versus rural,

temperate versus tropical climates, all areas of the country) and why does the FDA consider geographic diversity a goal? Beyond "improving demographic diversity," should sponsors aim for 50% urban and 50% rural, or should they aim for sufficient geographic diversity to ensure that other epidemiologic factors are addressed, and if so, which ones?

6. In addition to considering clinical sites in geographic locations with higher concentrations of racial/ethnic minorities, we recommend considering diversity when selecting study coordinators, in addition to health care providers, to conduct studies (lines 247-248). In particular, study coordinators and investigators are the face of the study to the participant especially with respect to languages spoken at a site, and efforts to increase the diversity of the research team itself should be encouraged.

    a. We recommend FDA create a tool to overlay the census data (in the US) with disease prevalence. This tool would help to identify geographic density, at least in certain dimensions, and it would enable considerations of appropriate site selection. Leveraging ClinicalTrials.gov for this purpose would also strengthen the utility of this federal resource for stakeholders.

7. Consistent with the point above, investigators play an important and pivotal role in securing diverse patients and ensuring that the study is representative of the population of the disease. Specific recommendations to assist investigators in recruiting and retaining representative populations would be welcome. The benefits of training investigators and their research staff in cultural competence and in methods to expand recruitment and returning during selection, start-up, and conduct of the trial should be mentioned. The sponsor can emphasize to selected sites the importance of including diverse participants within the clinical study, including factors that may not explicitly be addressed by the protocol eligibility criteria.

C. Specific comments and questions on the draft recommendations

1. We support the idea that the epidemiology of the disease should be used to inform recruitment strategies and the research plan. Ideally, recruitment of study populations with demographic characteristics that are representative of those who are likely to have access to the product should be built into research proposals and inform FDA oversight. The Agency could recommend diversity be specifically addressed within the sponsor's target product profile (TPP), a tool specifically endorsed by FDA within the draft guidance on "Target Product Profile — A Strategic Development Process Tool." We suggest that the current FDA guidance be explicit in recommending that the recruitment plan consider elements of diverse representation, when relevant. If considerations of diversity are not relevant, necessary, or feasible for a given drug, condition, or trial, a specific statement and explanation as to why should be included. While attention to diverse representation in clinical trials is important, we do not believe that specific quotas should be suggested or mandated as trials would fail if specific target are not met. The

necessity of bringing novel therapies to market in a timely fashion must be considered and balance the drive to diverse inclusion.

2. The FDA guidance makes reference to the FDA guidance on "Collection of Race and Ethnicity Data in Clinical Trials (October 2016)" on inclusion of a "plan to address the inclusion of clinical relevant populations with the Agency" (line 361-362).

    a. It would be helpful for the FDA to provide further guidance on the elements and expectations of a model recruitment and retention plan within this current guidance document or in a subsequent guidance.

    b. If the recruitment plan includes the intention to recruit a diverse population by demographic, monitoring against that plan should be expected. Guidance on monitoring would be helpful.

    c. Additionally, recommendations for corrective actions to rebalance the intended participant populations when the goals of the recruitment plan are not achieved during trial conduct would be helpful.

    d. It would be helpful to discuss the role and responsibilities of the data monitoring committee (DMC or DSMB) in reviewing concordance with the plan.

3. The guidance lists two specific methods to render trial participation less burdensome for participants (line 210ff). It would be helpful to include a third method that specifically relates to the burden of understanding what potential and enrolled participants experience when processing technical and scientific information, especially when delivered in the context of a new, serious, or complex medical diagnosis. A commitment to health literacy in all participant-facing clinical research documents is important as well as training of the clinical research workforce in health-literate communications, including considerations of cultural and linguistic differences.

4. Many of the recommendations and examples are rather general and will be difficult to apply without greater specific guidance. Further, scientific and other questions arise that would benefit from greater clarity, many of which relate to the research plan, sample size, and statistical analysis plan:

    a. The statistical implications of each of the FDA recommendations should be addressed.

    b. Sample size calculation is not mentioned in this guidance. Should the sample size be increased when including a more diverse population as inclusion may lead to greater variability in the data and outcomes (and see more specific comments and examples below)? How big is big enough? Should trials be stratified for demographic factors that are likely to have a major impact on response to therapy, and how will that impact the timeline and cost of product development?

c. How does the FDA consider the importance of diverse representation across the product development lifecycle, from phase 1, 2, and 3 trials to post-approval studies? FDA has required a plan at the end of phase 2 for race and ethnicity, but what about other dimensions of diversity? For efficiency of product development, does FDA assign greater importance to diverse representation of participants in Phase 3 and post-approval studies?

d. The FDA suggests protocol modifications with respect to eligibility criteria during trial conduct (lines 119-120). Do these changes need to be pre-specified in the protocol and the study powered for an interim analysis? Would such protocol modifications also require results before and after the amendment to assess its impact?

e. The FDA suggests inclusion of "children … and adolescents … in confirmatory clinical trials when appropriate" (line 132). FDA references prior guidance for oncology trials. Guidance on inclusion of children and adolescents with diseases in other therapeutic areas would be helpful. Under what criteria would it be appropriate to include children in a confirmatory phase 3 trial? Do the considerations change if the dosage differs for children? And if children receive a different dose, would the overall results of the trial be generalizable to the entire population? Should children be analyzed as a separate subgroup or as part of the overall population? We anticipate that a subgroup analysis would be important in this case – would the interpretation of an apparent difference in effect in children be treated the same as it would in other subgroups, or is the possibility of effect modification assumed to be greater in this case? Further, what are the implications for enrollment numbers and would the trial need to be powered for such subgroup analysis? Finally, consideration of when it would be appropriate to include children and adolescents in trials other than confirmatory would be helpful.

f. Section II.A, Broadening Eligibility Criteria in Enriched Clinical Trials (line 76): the first paragraph provides a detailed discussion of enrichment in trial design. In the 2nd paragraph, the FDA advises "that a reasonable sample of participants who have the disease but do not meet the prognostic or predictive enrichment characteristics prespecified in the clinical trial" should be included. This paragraph stops short of advising sponsors on how to broaden eligibility criteria in Enriched Clinical Trials, as the title of this section implies.

g. Encouraging the use of enrichment strategies appears to be a different approach than limiting exclusion criteria. It would be helpful for the FDA to give more specific guidance, both in study design and statistical analysis of expansion cohorts.

    i. When (e.g. phase 2 or 3) should enrichment strategies be considered? If enrichment is used in phase 3 trials, can the "primary population" or the

primary endpoint differ from the intention to treat (ITT) population leading to a different population being studied for safety and efficacy? The guidance implies that the broader participant group may be considered "as part of the secondary efficacy and safety analyses" (line 167-8), but no analysis of the impact on enrollment numbers or ITT is mentioned.

ii. What are the statistical considerations for this analysis? How should an "expansion cohort" be treated statistically in the context of, or separate from, the primary study population? What are the implications for sample size and study design? In other words, is the enriched population only included for purposes of secondary efficacy and safety (line 168) and not the primary endpoints of the trial?

h. Section B.2 *Trial Design and Methodological Approaches* includes a consideration of adaptive clinical trials, with an interim analysis from the trial and external data. Would such interim analyses require unblinding? Would the alpha level need to be adjusted? How can bias be avoided with results shared during trial conduct (lines 152-156)?

i. What is the role of the data monitoring committee (DMC) in the modifications to trial design and methods approaches? When and how (in the absence of statistical power) should DMC guidance include a review of subgroups for safety and efficacy? In the section of the draft guidance on adaptive trial design, would the DMC make the decisions related to population broadening?

ii. Indeed, we consider the treatment of adaptive clinical trial design in the guidance to be insufficient and perhaps impractical. If the trial begins with a narrow population due to concerns about safety or efficacy in an excluded population, then interim results will not be helpful. And if the trial starts with a broader population, the interim results in a small subpopulation of concern are unlikely to be precise enough to draw conclusions. Further clarification of the issues involved in adaptive clinical trials would be instructive.

i. There is a proposal to include a broad population in the trial following a primary analysis on a narrower population. Presumably, a positive primary analysis would allow approval of the product for the narrower population. What would be the criterion to permit approval in the broad population: a significant pooled analysis? Significance in the additional patients alone? Some assessment of consistency between the narrow population and the additional patients? It would be helpful for the guidance to address this.

j. The inclusion of pregnant women (lines 178-185) raises interesting derivative questions. Does the Agency envision that a study with an investigational product

could have "sufficient assurances of safety during pregnancy" (line 179-180) or only a marketed product? Will contraception continue to be required for women of child-bearing-age in a trial determined to have assurances of safety during pregnancy, since impact of the product on conception and the first month of life may not be known? What are "sufficient assurances of safety during pregnancy" for investigational products that have not been used in pregnant women previously? Does the FDA suggest PK sampling of the same woman in each trimester to control for intraparticipant variation? How can one minimize the number of individuals burdened by PK studies?

k. The comments regarding re-enrolling participants in rare disease trials require careful consideration (lines 310-320), since only the patients who benefitted from the investigational product and/or for whom it was safe would be considered for entry into a later phase trial (usually phase 3). Thus, selection bias will exist. What are the methodologies to "avoid selection bias" as suggested at line 317-318?

    i. Wherein the same patient is in multiple trials, how should pooled safety analyses at the product level be reported (e.g. investigational brochure, Development Safety Update Report, Periodic Benefit-Risk Evaluation Report)?

    ii. Can the same patient entered twice in the product development program be considered independent? How should the statistical analysis plan be to accommodate this issue?

l. Many of the participant-engaged and patient-centric suggestions listed appear consistent with the principles of pragmatic clinical trials. It would be helpful to expand upon the use of pragmatic clinical trials as a possible path to increasing diversity. Indeed, we believe that the role of participant/patient/public engagement throughout the clinical trial planning and conduct process could be expanded in the document, and reference to the FDA guidance on Patient-Focused Drug Development would be helpful.

m. Many of the directives of the draft guidance would be enhanced by specific case studies of success, specifically addressing modifications that have been made to increase diversity, and accommodations to study design, sample size, and statistical plan, if necessary.

n. Whenever statistical analysis is not possible, the guidance should comment on the analysis and interpretations -- and limitations thereof -- of data collected from diverse groups when numbers are small.

D. Additional Considerations

1. Populations studied and data collected in early, pre-approval clinical trials will always be limited, particularly with respect to subpopulations. The guidance should underscore the importance of balancing the time and financial resources required in the investigational, pre-approval stage of product development with the urgency of getting new products to market, particularly in the case of unmet medical need or significant advantage (e.g. increased benefit, decreased risk, ease of administration, etc.) over currently available treatments.

2. We recommend that the FDA address the use of real-world data (RWD)/real world evidence (RWE) to help collect clinical data in diverse patient populations, particularly for later phase studies and potentially to decrease the number of subjects needed for clinical studies. For example, treatments used in routine clinical practice in certain patient populations (e.g., pediatric or elderly) not studied in the clinical program could further inform benefit and risk profiles. RWD/RWE allows for the collection of longitudinal data for all patients, pre- and post-approval, for the purposes of informing clinical trial design for diverse participants, the use of the product across diverse populations, and other goals. We believe that RWD/RWE could potentially complement, support, and extend the findings of a clinical trial, while increasing the number and diversity of patients studied.

3. We recognize that the FDA must use the OMB racial categories by law; however, the OMB categories were not specifically created for use in the clinical trial setting and are unwieldy. For example, a large and growing number of Americans are multi-racial; the OMB categories simply do not fit that reality. Additionally, given the globalization of clinical trials, the OMB categories do not represent concepts of race and ethnicity outside of the US, so it is difficult for sponsors to standardize racial/ethnic categories accurately or align them with OMB categories appropriately. Currently, mapping to the five OMB categories is accomplished by study sponsors prior to submitting data to the US FDA. We recommend that FDA consider creating a new more comprehensive, and high-level, standardized set of global racial and ethnic categories, ideally in collaboration with other global regulatory agencies. A new framework would improve the quality of demographic data currently being submitted to global regulatory authorities, and alignment would allow interoperability and integration of the data.

Corrections

- Reference 17 provides a link to the "Public Workshop: Evaluating Inclusion and Exclusion Criteria in Clinical Trials." This link takes a viewer to an FDA website of Reports and Plans Mandated by FDARA. The link provided under the heading "FDARA Section 610 convene a Public Meeting" take the user to a dead link. The webpage says "Page Not Found."

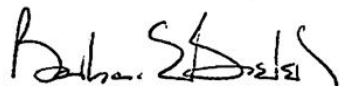
- Section II.A, Broadening Eligibility Criteria in Enriched Clinical Trials: Reference #9 cites the December 2012 draft guidance for *Industry Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. It appears this guidance for industry has been finalized and we believe should cite the March 2019 guidance titled *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products.*

- *Typographical error*: we believe footnote 20 should reference January 2018 not 2019.

Thank you again for the opportunity to comment on this important issue. We believe that by including or addressing the issues outlined above, a revised version of the guidance will provide focus and clarity to the issue of diverse enrollment in clinical trials, an issue of significant impact for the evaluation of biological efficacy and safety of interventional products and understanding of biologic variability.

The MRCT Working Group is comprised of a broad cross section of relevant stakeholders, but we do not profess to represent those individuals or their organizations. We are available to discuss our comments with you if that would be helpful and would be happy to work with you on any of the aforementioned items. Please feel free to contact the MRCT Center at bbierer@bwh.harvard.edu, sawhite@bwh.harvard.edu, and mark.barnes@ropesgray.com.

Respectfully submitted,



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