BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

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

June 26, 2020

Submitted electronically at www.regulations.gov

The Honorable Stephen Hahn, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20990

RE: Docket No. FDA-2019-N-4824, Office of Minority Health and Health Equity Strategic Priorities; Establishment of a Public Docket; Request for Comments

Dear Commissioner Hahn:

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 request for input and comments on strategic priorities for the Office of Minority Health and Health Equity (OMHHE). In making these comments, we note that the MRCT Center has collaborated with the OMHHE over the last two years on an MRCT Center initiative focusing on diversity, inclusion, and equity in clinical research. We offer the comments here independent of that collaboration and work; we have not discussed these comments with anyone in OMHHE or more broadly at the FDA, nor mentioned that we will be responding to the request for comments. The responsibility for the content of this document rests with the leadership of the MRCT Center and not with the institutions affiliated with the authors.[1]

The MRCT Center is a regulatory 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 ex-U.S., in-country engagements and has a long-standing commitment to training global regulators, investigators, and others. As mentioned, over the last two years, the MRCT Center convened a working group to address the challenge of diverse representation in drug development and in clinical research more generally. Within the next month, the MRCT Center will forward to FDA the guidance document that we are just completing, and we will not repeat here the recommendations that we intend to make in that guidance document.

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

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Particularly in this time of heightened awareness of structural and systematic racial prejudices and health inequities, the work of the OMHHE could not be more important or timely. The MRCT Center applauds the FDA's commitment to strengthening the office, reviewing its strategic priorities, and, we trust, enhancing the visibility of FDA's commitment to diversity and inclusion. We appreciate that the mission of the FDA, at least in part, is the evaluation of biological efficacy and safety of medical products that make claims about health; in this context, an understanding of biologic variability in diverse populations is properly regarded as part of the core mission of the FDA. Evidence-based conclusions about safety and efficacy can only be made by collecting and analyzing robust data that examines the heterogeneity of effect in diverse populations. Increasing the diversity of individuals participating in clinical trials is not only important for the understanding of biology but also to promote public trust.

We have several suggestions for consideration by the FDA:

1. Data-driven evidence is most useful to propel change and improvement. The data, however, must be collected in a common format with a common data dictionary and metadata. A new framework would improve the quality and interoperability of demographic data. There is significant work that remains to be done to establish common data standards and metadata for dimensions of diversity. OMHHE should work with OMB and other agencies, sponsors, academia, and patients/patient advocates from diverse communities to:
    a. Review and update the OMB categories of race and ethnicity, including considerations of north African populations, Asian populations (East Asian versus South Asian for instance), multiracial identities, and other demographic complexities to reflect current views that are respectful and reflect individual self-identification.
    b. Establish terms for race and ethnicity that will resonate globally and will allow common data collection in multinational trials. Optimally the categories adopted by the FDA would be developed with international health regulatory authorities, as alignment would allow interoperability and integration of the data.
    c. Establish common definitions of social determinants of health (SDH) in all its dimensions and develop validated measures for collecting that data.
    d. Establish data standards for gender, as distinguished from sex.
    e. Develop a common template and technical solution for collecting and reporting demographic information such that the data can be used with minimal effort.
2. Promoting demographic diversity in clinical trials has been a focus of the FDA, as has a commitment to transparency of the data collected. We believe that the OMHHE should oversee and strengthen annual surveillance of race, ethnicity, age, sex, gender, and social determinants of health (SDH) of participants in clinical trials and publish their analyses that extends beyond the very helpful data presented in Drug Trial Snapshots. The data should be granular, complete, and categorized to separate U.S. from ex-U.S. sites. This is particularly important as the data are often cited to demonstrate underrepresentation of Black/African American and Hispanic populations, despite the fact that these are multinational trials wherein individuals outside US do not self-identify with the OMB

categories, and the U.S. public should be able to see clear statements of U.S. data. This is not to suggest that FDA change its guidance on acceptance of foreign data: it is an issue of transparency and clarity. The trials upon which the data are drawn should be identified by the ClinicalTrials.gov Identifier (NCT number) for additional transparency and to permit the public to look further into the specifics of trials.

3. Drug Trial Snapshots has been and remains an important advance to illuminate and focus upon demographic representation in clinical trials. Drug Trial Snapshots, however, have not included all products reviewed and approved by the FDA (nor all trials other than pivotal ones). We suggest that representation in other trials (e.g., device trials) be included in this resource, and in the further development of the report made here.
4. Many industry-sponsored trials are conducted on products in addition to the registration trials reported in Drug Trial Snapshots. The data from those trials, almost all of which are submitted to the FDA, should be reflected in a more fulsome presentation of the data for the public.
5. The enrollment of each completed trial should be publicly posted and searchable by race, ethnicity, age (in categories), sex, gender, and other demographic and non-demographic variables, by country and optimally by site. Whether this searchable resource is within Drug Trial Snapshots or ClinicalTrials.gov directly, or both, is an answer for OMHHC to determine. Further, the agency should require the submission of demographic data of participants who completed the trial. Disproportionate dropout will affect the results but not the enrollment figures. What can be measured can be improved. Simply making the data visible, in our opinion, will begin the process of change.
6. Few Phase 3 registration trials have sufficient enrollment of diverse populations to allow analyses of those data by demographic, leading the approved label to reflect the insufficiency of data. This is accurate but leaves clinicians and the public without affirmative information on safety and efficacy of those populations. The OMHHE should work with other branches of the FDA to explore how to develop robust methods of evidence of efficacy and safety, and then should review post-approval analyses of data. Those data could include additional clinical trial data. Whether and how analyses of (reliable, fit-for-purpose) real world data (RWD)/real world evidence (RWE) may be helpful in that regard is an open but obvious question. For example, treatments used in routine clinical practice in certain patient populations (e.g., pediatric, elderly, Latino, Black) not studied adequately in the clinical development 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 the product development program. Agency guidance is needed.
7. OMHHE should work with other offices and centers in the FDA to ensure that genetic data used for product development or research adequately represent the diversity of the population. Issuance of guidance on the sufficiency or representativeness of diversity would be helpful.

8. OMHHE should work with other offices and centers in the FDA to ensure that algorithms and machine learning methods used for medical products interrogate databases that are representative. Methods to illuminate bias should be developed and communicated. The FDA and OMHHE might consider the development of data sources that are representative for relevant confirmatory analyses.
9. OMHHE has invested resources to create educational materials to introduce the public to the value and meaning of clinical research and these are available on its website. We believe that the FDA OMHHE should continue to expand this effort, for example, by translating into other common languages of the U.S. in addition to those currently available in English and Spanish.
10. The OMHHE is in a perfect position to develop materials for medical students, future investigators, and other stakeholders involved in the clinical trial enterprise to advance education on diversity and inclusion in clinical trials would be helpful. OMHHE outreach to institutions of higher learning, professional societies, patient advocacy and other non-profit organizations and others will help to prioritize the topic in curricula and continuing education.
11. The OMHHE has initiated some programs to engage minority communities directly. These efforts should be expanded, and resources provided. Exploration of what successful engagement should look like and elements and metrics of success would be useful. Further, thinking through strategies to organize community response and contribution to the clinical research enterprise are necessary: organizing engagement is preferable to the situation wherein every academic health center, every pharmaceutical and biotech company, and every investigator, however well-meaning, independently approach each community, thereby taxing the very resources that are meant to help.
12. FDA could advance understanding of clinical trials and research by requiring all patient-facing materials to be health literate. Many documents of instruction are not currently health literate (e.g. plain language, numeracy, design, imagery). OMHHE is positioned to develop methods and resources as to how industry can evaluate and demonstrate the health literacy of materials.
13. On the same theme, OMHHE could review the product labels and patient facing information for health literacy and simplification.
14. It is important for the Agency to disseminate successful approaches to recruitment and retention of underserved and underrepresented populations, not only by race and ethnicity but also by sex, gender, age, and economically- and educationally-disadvantage. Considerations, provided here as examples only, might include:
    a. Financial reimbursement and compensation for participation.
    b. Optimizing requirements of the clinical trial to minimize onsite visits, increase telehealth and home visits, and permit research procedures (e.g., imaging studies, blood draws) to be conducted locally rather than at the research site.
    c. Deploying technical solutions to permit remote data entry and remote monitoring and allowing the provision of technologies (e.g. wearables, tablets, etc.) without considering that provision undue inducement or a potential kick-back.

15. OMHHE should be allocated funds to manage an independent grant portfolio so that practices and guidance are based on robust evidence. The focus of the grant portfolio should align with the mission of the office, including the development of evidence for successful practices and methods for regulatory science of subgroups and subgroup analyses, recruitment and retention of underserved and underrepresented populations, outreach and education of diverse communities, community engagement and of its impact, changes in study design and conduct that foster inclusion while retaining data integrity, implicit bias and cultural competence training, and workforce development of underrepresented minorities in the clinical research enterprise. Grants should include multi-year projects to permit complex questions to be addressed. Additional grant funding could be made available to:
    a. Pipeline programs, to support early and mid-career training opportunities to help increase the diversity of the future clinical trial workforce.
    b. Development of a scientific program, similar to the Centers of Excellence in Regulatory Science and Innovation to focus on the regulatory science of minority populations, in all dimensions of minorities (e.g., impacts of social determinants of health), including the development of an evidence base for recruitment and retention of underserved and underrepresented populations, the development of data standards, etc.
    c. Development of a program of Centers for Clinical Investigation in minority health centers.
    d. Development of strategic public-private partnerships to advance the mission of the OMHHE.
16. In the end, what matters is increasing the inclusivity of clinical trial participants, across the many dimensions of diversity. Whether the mechanism to do so involves guidance, mandates, regulatory changes, or incentives is not clear and may benefit from further analysis. OMHHE is well-positioned to provide oversight of or conduct that analysis. For instance, would an incentive program to encourage greater diversity in clinical trial populations by providing patent protection extension be successful? Has the equivalent to encourage inclusion of pediatric populations had impact? Any program must require reporting of race and ethnicity of enrolled and retained clinical trial participants and should be based on the product development program not on one trial. Further, we believe that consideration of a time-limited program may be warranted. At the end of five years (or some date certain), the patent protection program would end, and thereafter expectations of or requirements for inclusion would be introduced.
17. Given the strategic importance of the work with which the OMHHE will be engaged, both in coordinating with other federal agencies, within the FDA, and independently, we believe an investment should be made to increase the size, visibility, and autonomy of the Office. At no time has there been a greater focus on issues of structural and systemic racism in the US and globally, and this is a moment to position the FDA, and OMHHE, to advance the evidence base that will promote health equity, justice, and public health.

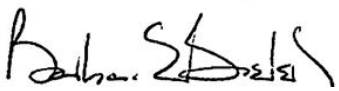
Thank you again for the opportunity to comment on this important issue, for developing the strategic priorities for OMHHE to help provide focus and clarity to the issue of diverse enrollment in clinical trials, an issue of significant impact for the evaluation of biological efficacy and safety of interventional products and understanding of biologic variability. We are encouraged by the proactive efforts of OMHHE and the FDA to address these salient issues.

The MRCT Center and the "Diversity" 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 or Barbara Bierer, MD, bbierer@bwh.harvard.edu; (617) 827-7413.

We look forward to continuing our partnership with the FDA and with OMHHE. We are at your service should we be able to be helpful.

Respectfully submitted,



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