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

To Whom it May Concern:

This letter represents comments submitted on behalf of the **Digital Medicine Society (DiMe)** for consideration by the U.S. Food and Drug Administration (FDA) regarding Docket No. FDA-2021-D-0789 for "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry; Availability."

DiMe is a 501(c)(3) **non-profit organization** dedicated to **advancing digital medicine to optimize human health**. We do this by serving professionals at the intersection of the global healthcare and technology communities, supporting them in developing digital medicine through interdisciplinary collaboration, research, teaching, and the promotion of best practices.

Founded in 2019, DiMe is the first **professional organization** for experts from all disciplines comprising the diverse field of digital medicine. Together, we drive scientific progress and broad acceptance of **digital medicine to enhance public health**.

DiMe convened experts from across the clinical trials ecosystem to develop resources to support and advance inclusion of underrepresented patient segments in digital clinical trials. This project, "Diversity, Equity, and Inclusion in Digitized Clinical Trials"[1] is an unique opportunity for the development of best practices, pragmatic resources, and educational materials to support life science companies to identify approaches to clinical study design and implementation. Broad dissemination and adoption of resources developed by this interdisciplinary team will provide a shared foundation for clinical trial

[1] Digital Medicine Society. Diversity, Equity, and Inclusion in Digitized Clinical Trials. https://www.dimesociety.org/tours-of-duty/diversity-equity-inclusion/

development teams to advance digital medicine research in an effective and equitable manner. The following comment leverages the combined expertise of our project team regarding diversity in clinical trials. We appreciate the opportunity to offer our comments on this draft guidance document.

In alignment with DiMe's mission, we appreciate that this guidance was issued by multiple centers: Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), and Office of Minority Health and Health Equity (OMHHE). In particular, we are pleased to see the importance and urgency that is being placed on the issue of lack of diversity in clinical trials.

We applaud FDA's recognition of the **challenges** facing clinical trials and **FDA's commitment to providing specific and deliberate recommendations** to sponsors throughout the process of developing medical products. **Enrolling participants** from **underrepresented racial** and **ethnic populations**, **representative** of the population of the United States, is imperative for **advancing healthcare,** fundamental to **public health**, and a priority for **addressing health inequities**. Simultaneously, the use of digital medicine products as drug, biologic, and device development tools is growing rapidly. Without proper investigation into how digital medicine products function with diverse groups of people, the digitization of clinical trials may fail to realize the promise of easier access, broader inclusion, and more generalizable findings. Worse, broad adoption of digital tools in clinical trials may amplify historic, persistent, and preventable health disparities. This comment focuses on the issues at the intersection of diversity, equity, and inclusion in clinical trials and the digitization of these same trials.

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Comment Structure

Our comment is structured around feedback and questions that we have received from members of the "Diversity, Equity, and Inclusion in Digitized Clinical Trials" project team[2]. We do not presume to provide answers; that is the sole domain of the Agency. Rather, we spotlight specific elements in the draft guidance and provide suggestions from our community of experts.

Purpose and Need for this Draft Guidance

Lines 16-28 indicates that the purpose of this guidance is to provide recommendations to sponsors for Developing a Race and Ethnicity Diversity Plan (referred to as the "Plan") to enroll participants from underrepresented racial and ethnic populations. We agree that a Plan is needed to fill current knowledge gaps on the safety and efficacy outcomes that may be associated with specific populations and to ensure that those populations who can benefit from the medical product will have access to it. We appreciate the FDA's acknowledgement that "the lack of representation of these populations in clinical research reflects, in part, a broader issue regarding differential access to health care," (lines 106-109). The differential access to care is a major barrier for many populations; specific mention of this in the draft guidance highlights **the urgency to rectify the problem of a lack of racial and ethnic minorities in clinical trials**.

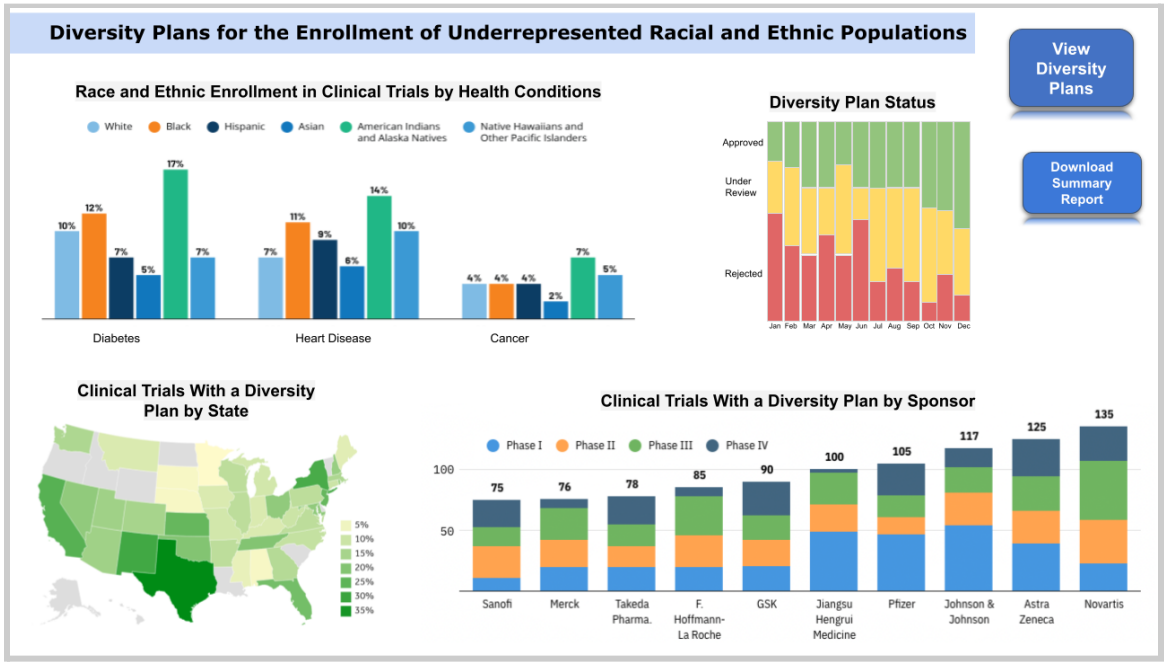
Lines 60-65 indicates that the draft guidance document does not have the "force and effect of law" and the "guidance should be viewed only as recommendations." We understand that the FDA is not positioned to mandate any guidance. However, given the current underreporting of race and ethnicity data by clinical trial sponsors,[3] and the lack of representation of racial and ethnic populations in "biomedical research despite having a disproportionate disease burden" (lines 21-23), **this draft guidance and recommendations** for a Plan **is an opportunity to significantly affect change**.

While the FDA cannot mandate that sponsors use this Plan, there are measures that the FDA can implement that may influence sponsors willingness to adopt the Plan as a part of their workflow. We recommend

[2] Digital Medicine Society. Diversity, Equity, and Inclusion in Digitized Clinical Trials. https://www.dimesociety.org/tours-of-duty/diversity-equity-inclusion/
[3] Turner BE, Steinberg JR, Weeks BT, Rodriguez F, Cullen MR. Race/ethnicity reporting and representation in US clinical trials: A cohort study, The Lancet Regional Health - Americas, 2022. https://doi.org/10.1016/j.lana.2022.100252.

- A publicly available dashboard which shares the Plan submitted by sponsors during their IND or IDE submissions. All applications should be included on the dashboard for applications which were rejected and accepted, showing the enrollment targets for all populations. The dashboard should be updated at some predetermined interval to display the enrollment progress. The current FDA public database of post marketing recommendations[4] provides precedent for this type of sharing. A sample dashboard is presented in figure below; all images are hypothetical.
- An annual report or annual data snapshot summarizing which sponsors submitted a Plan, for which clinical trials and the enrollment targets.
- An annual report summarizing the operational measures supporting Plans by different sponsors.

We are confident that this type of **public accountability** will reinforce the severity of the challenges and demonstrate a **strong commitment** to **improving public health** through **increased participation** by **all groups that can benefit** from the clinical trial. If intentional, public attention is given to the efforts underway this will positively impact those conducting and participating in clinical trials and will ultimately lead to more reporting on race and ethnicity, and participation by more groups.



[4] https://www.accessdata.fda.gov/Scripts/cder/pmc/index.cfm

Content of the Plan and Enrollment Goals

Lines 171-182 recommends enrollment goals that are based on protocol objectives and potential for differential safety and effectiveness within different populations. Lines 189-193 indicate that race should also be assessed with other covariates that may affect the safety and effectiveness of the medical product. While these details are important for a thorough understanding of the medical product, we propose that these fine details should be a second level, and focus should be placed on race and ethnicity as the first level of tackling underrepresentation. Importantly, the current state of clinical trials is such that people of color represent only 2% to 16% of patients in clinical trials.[5] Data on diversity and inclusion from FDA's 2020 data snapshot[6] indicates that **of 32,000 clinical trials participants, only 11%** were **Hispanic** and **10%** were **Black or Asian**. Additionally, **Blacks and Hispanics experience disproportionate disease burden**,[7,8] that continue to be exacerbated by social determinants of health.[9] The lack of diversity in biomedical research has also hindered our understanding of disease etiology, diagnosis, and treatment options.[10] Furthermore, the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11)[11] requiring race and ethnicity reporting in ClinicalTrials.gov for clinical trial participants was intended to address these knowledge gaps. However, Blacks continue to be underrepresented in clinical trials, despite a 19% higher incidence rate.[12]

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[5] Flores LE, Frontera WR, Andrasik MP, et al. Assessment of the Inclusion of Racial/Ethnic Minority, Female, and Older Individuals in Vaccine Clinical Trials. JAMA Network Open. 2021;4(2):e2037640. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776562.

[6] FDA's 2020 Drug Trials Snapshot Summary Report. https://www.fda.gov/media/145718/download.

[7] Ellis KR, Hecht HK, Young TL, Oh S, Thomas S, Hoggard LS, et al. Chronic Disease Among African American Families: A Systematic Scoping Review. Prev Chronic Dis 2020;17:190431. https://www.cdc.gov/pcd/issues/2020/19_0431.htm.

[8] McGrath RP, Snih SA, Markides KS, et al. The burden of health conditions across race and ethnicity for aging Americans: Disability-adjusted life years. Medicine (Baltimore). 2019;98(46):e17964. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6867730/.

[9] Gómez CA, Kleinman DV, Pronk N, et al. Addressing Health Equity and Social Determinants of Health Through Healthy People 2030. J Public Health Manag Pract. 2021;27(Suppl 6):S249-S257. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8478299/.

[10] Fatumo S, Chikowore T, Choudhury A, Ayub M, Martin AR, Kuchenbaecker K. A roadmap to increase diversity in genomic studies. Nat Med. 2022;28(2):243-250. https://pubmed.ncbi.nlm.nih.gov/35145307/.

[11] https://clinicaltrials.gov/ct2/about-site/background.

[12] Kelly M. Herremans, Andrea N. Riner, Robert A. Winn, Jose G. Trevino. Diversity and Inclusion in Pancreatic Cancer Clinical Trials. Gastroenterology 2021, 161(6): 1741-1746. https://www.sciencedirect.com/science/article/pii/S001650852103345X.

For these reasons, we propose that the FDA recommend that enrollment goals prioritize those identifying as Black or African American, Hispanic/Latino, Indigenous and Native American, Asian, Native Hawaiian and Other Pacific Islanders, and other persons of color. These populations should be overrepresented in the enrollment goals. The urgency to prioritize race and ethnic groups historically underrepresented in biomedical research mirrors approaches by other government agencies, specifically the NIH's *All of Us Research* Program, the cornerstone of the Precision Medicine Initiative.[13] **There is a desperate need for drastic measures to ensure that these populations are included in clinical trials and have the opportunity to benefit from new and existing medical products.** This should be the first level of defining the enrollment goal. Special emphasis should also be placed on disease incidences and prevalence to reflect those most impacted and living with the disease burden, for example higher incidence rates of breast cancer[14] among Black women. Enrollment goals can then be further refined when sufficient data on safety and efficacy for relevant race and ethnic populations become available.

We recognize that there is also a need for "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" (lines 33-36). However, given that the previous guidance has called for diversity and very little progress has been made, **there is a critical need to prioritize race and ethnicity**. Many of these additional groups will be captured, organically, when focusing on race and ethnicity. We request that the final guidance for the Plan specifically states that the Plan should focus on race and ethnicity.

We also recommend that sponsors identify historical data sets that have been attributed to certain disease factors and how their enrollment goals and diversity plans will satisfy an overall increase, by percentage, of inclusionary participants to be qualified within their studies.

[13] Mapes BM, Foster CS, Kusnoor SV, et al. Diversity and inclusion for the All of Us research program: A scoping review. PLoS One. 2020;15(7):e0234962. https://pubmed.ncbi.nlm.nih.gov/32609747/
[14] Howard, FM, Olopade OI. Epidemiology of Triple-Negative Breast Cancer A Review. The Cancer Journal 2021, 27 (1): 8-16. https://pubmed.ncbi.nlm.nih.gov/33475288/.

Implementation of the Plan

Lines 90-97 recommends that sponsors include operational measures "that will be implemented to ensure diverse clinical trial participation." We applaud the inclusion of this additional recommendation as it allows sponsors to **show a genuine commitment** to the Plan, by **going beyond arbitrarily filling out a table** with enrollment goals for underrepresented populations. Operational measures to support the Plan shows strong commitment to the inclusion of groups who can benefit from the medical product and to the advancement of scientific knowledge for the health condition being studied.

We recommend that the **FDA request a highly detailed operational measures strategy** that includes support for the inclusion of racial and ethnically diverse patients throughout the clinical trial process – from participant engagement and enrollment to retention and study completion, as baseline. The operational strategy should then be customized for each underrepresented race/ethnic group. Sponsors should include a detailed proposal, beginning with which clinical research teams will be invited to participate in the trials and why they were selected, the resources and processes dedicated to identifying diverse site investigators and clinical trials teams, and how sponsors will engage and support those researchers. The race and ethnicity of the enrollment site team may limit the types of patients enrolled in the study[15]; therefore the diversity of the site team should be an essential component of the Plan. We also propose that **sponsors be innovative with participant engagement and enrollment mechanisms**, including efforts to engage and include non-academic research centers (for example Federally Qualified Health Centers, community care organizations, etc.), and efforts to decentralize and digitize workflows and processes.[16] Decentralization of clinical trials is already proving successful with increasing access and diminishing participation burdens, and improving overall logistics for the clinical team.[17] Decentralization also allows participants to remain in environments with which they are

[15] The Tufts Center for the Study of Drug Development (Tufts CSDD). New Study Finds Site Personnel Race and Ethnicity Highly Correlated with Diversity of Patients Enrolled. November/December 2021 Vol. 23(6). https://f.hubspotusercontent10.net/hubfs/9468915/Impact%20Report%20Preview.png

[16] No place like home? Stepping up the decentralization of clinical trials. Mckinsey and Company. June 10, 2021. https://www.mckinsey.com/industries/life-sciences/our-insights/no-place-like-home-stepping-up-the-decentralization-of-clinical-trials.

[17] Van Norman GA. Decentralized Clinical Trials: The Future of Medical Product Development?∗. JACC Basic Transl Sci. 2021;6(4):384-387. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8093545/.

comfortable and to stay connected to healthcare providers who they already trust.

We also endorse the recommendation that operational measures should "include, but are not limited to offering financial reimbursement for expenses incurred by participation in a clinical trial or study (e.g., travel or lodging), providing language access to participants with limited English language proficiency, and partnering with community-based organizations to provide support to study or trial participants" (lines 93-97).

The Digital Health Measurement Collaborative Community (DATAcc), hosted by the **Digital Medicine Society (DiMe)** developed a **toolkit** with specific resources to support **more inclusive** approaches to **delivering healthcare** or **conducting research**.[18] This toolkit provides support for the clinical trial team that can be applied to existing workflows. While the toolkit is focused on delivery of a digital health measurement product, it does contain clear plans for community and participant engagement, and sustained community partnerships, in addition to resources to be shared with study teams and participants, that can be applied broadly. The inclusivity toolkit also applies to decentralized and digitized clinical trials, and provides resources and tools required to ensure clear communications, and to support and empower participants in their role in the clinical trial. The level of support provided in the inclusivity toolkit will allow sponsors to learn about participants' lived experiences and how this will impact their participation; this is a first step with building trust with participants.

While the **inclusivity toolkit provides the "how to" for operationalizing** and supporting the engagement, enrollment and retention of diverse participants, sponsors will need to make **a formal commitment** with **allocating funds to support these processes**. Funds will be required to alleviate any financial burdens on participants; this reimbursement system should be developed at the sponsor level in consultation with the individual clinical sites. Sponsors should also adequately budget for additional cultural support, such as translators.

An **evaluation component** should also be included in the operational measures strategy. Sponsors should evaluate the Plan, within their organizations and with the clinical sites and research teams, at specific intervals throughout the

[18] Digital Medicine Society, Digital Health Measurement Collaborative Community (DATAcc) Inclusivity Guide for Developing Community Partnerships. https://datacc.dimesociety.org/deployment/

clinical trial. The evaluation plan should include mitigation plans if the trial is not on track to meet the enrollment goals.

The table in the draft guidance (line 225), provides **a comprehensive summary** of elements to be included in the diversity Plan. We would like to see this table **shared publicly**; in annual reports, with the suggested dashboard and/or on ClinicalTrials.gov, and in industry publications. For the healthcare industry to make significant strides towards improved health care and health equity, this information, along with challenges and successes, must be shared, broadly.

Summary and Conclusion

We appreciate the recommendations provided in this guidance for a detailed diversity Plan and operational workflow. The **FDA's commitment to increasing race and ethnic diversity** in clinical trials **is inspiring**. In this comment we provide specific instructions to supplement the FDA's recommendations for traditional trials and encourage adoption of innovations for the digitization of clinical trials. Digitization will bring new, more robust tools and mechanisms for clinical trials[19]; now is the time for a paradigm shift to ensure that race and ethnic diversity is a standard of clinical trials.

With our additions to this draft guidance, **sponsors can** begin to **move the needle and affect considerable change** with increased representation of racial and ethnic groups, to advance health equity. Our aspiration is that regulators, industry, sponsors of clinical trials, and deployers of digital products for use in clinical trials will adopt and build on the recommendations described in this comment, to develop **a robust diversity plan** that will become **fundamental to all clinical trials,** including decentralized and digitized clinical trials.

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[19] Inan OT, Tenaerts P, Prindiville SA, et al. Digitizing clinical trials. NPJ Digit Med. 2020;3:101. Published 2020 Jul 31. doi:10.1038/s41746-020-0302-y