AGS Geriatrics Healthcare Professionals
Leading Change. Improving Care for Older Adults.

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September 26, 2024

Robert M. Califf
Commissioner
Food and Drug Administration,
Department of Health and Human Services,
Attention: FDA-2021-D-0789
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

SUBMITTED ELECTRONICALLY VIA
https://www.regulations.gov

Re: Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies; Draft Guidance for Industry; Availability (FDA-2021-D-0789)

Dear Commissioner Califf:

The American Geriatrics Society (AGS) appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) on the draft guidance document, "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies: Guidance for Industry." AGS is a nationwide not-for-profit organization dedicated to improving the health, independence, and quality of life of all older adults. Our 6000+ members include geriatricians, geriatrics nurse practitioners, social workers, family practitioners, physician assistants, pharmacists, internists, and others who are pioneers in advanced-illness care for older individuals, with a focus on championing interprofessional teams, eliciting personal care goals, and treating older people as whole persons. We provide leadership to healthcare professionals, policymakers, and the public by implementing and advocating for programs in clinical care, research, professional and public education, and public policy. AGS believes in a just society – one where we all are supported by and able to contribute to communities and where ageism, ableism, classism, homophobia, racism, sexism, xenophobia, and other forms of bias and discrimination no longer impact healthcare access, quality, and outcomes for older adults and their caregivers. We believe discriminatory policies—especially when they are perpetuated across the healthspan and lifespan—can have a negative impact on public health for us all as we age.

ACCOUNTABILITY: ADDRESSING AN IMPORTANT GAP IN THE DIVERSITY ACTION PLANS (DAP)

It is fundamentally important to ensure sponsors are accountable for enrolling participants that reflect the diversity of the intended patient population without inadvertently slowing research. AGS agrees with the DAP requirement that facilitating diverse recruitment would need to precede the enrollment. However, the DAP does not address consequences of failing to meet enrollment goals. We believe accountability would be best ensured through an enrollment analysis at the annual review of a sponsor's trial and potential consequences of failing to meet ultimate enrollment targets. AGS encourages that

inclusivity and representativeness be a criterion in the approval process, which can be done in a flexible way, so that drugs, medical devices, and interventions are safe and effective for all populations.

We also support accountability for manufacturers as part of post-marketing requirements when the FDA requires post-marketing studies. Without accountability, there would be no compliance. We believe that the failure to comply with the requirements should be met with penalties, including financial, labeling changes, removal from the market, or initial time-limited marketing approvals that would expire unless data is generated that supports the initial approval and the post-marketing requirements are judiciously applied.

GENERAL COMMENTS

AGS is fully supportive of the FDA working to improve enrollment of underrepresented populations in clinical studies for drugs, biological products, and devices with the goal of ensuring the safety and efficacy for the intended use population. In April 2024, we commented to the FDA on the importance of ensuring that clinical trials reflect the diversity of the population being treated and its role in ensuring that older adults, including those living with multiple chronic conditions, are represented in clinical trials.[1] We believe inclusivity and representativeness are the core of rigorous research and development of safe and efficacious drugs, medical devices, and interventions for all populations.

We appreciate the FDA's focus on improving enrollment of study populations in clinical trials to adequately reflect the larger population for which treatments are being developed and we see the DAP draft guidance as a significant tool to detect key differences in clinical effectiveness and safety. All too often clinical trials have underrepresentation of historically marginalized groups.[2,3] It is critically important to ensure the appropriateness of target populations to whom drugs, products, and devices are then marketed and provided to. When medical evidence is generated from study populations that are not reflective of most of the people who need the care, we miss opportunities to learn how to optimize health and resilience and avoid suffering. It is also vital to eliminate avoidable differences in health outcomes, as well as to consider and mitigate unintended consequences of changes in guidance.

Recent U.S. Census Bureau projections have shown the inevitable changing population of the U.S. that is older and more diverse.[4] Given the changing composition of the nation's population, study populations will also inevitably continue to change over time. We believe that part of the goal of collecting disaggregated data is to ensure all populations receive personalized care and with cultural humility. By capturing richer data, we may also weave a richer tapestry honoring individual subgroup cultures and traditions without eliminating cultural expressions.

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[1] American Geriatrics Society. Letter to FDA on Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products Draft Guidance. April 29, 2024. Accessed September 2024. https://www.americangeriatrics.org/sites/default/files/AGS%20Comment%20on%20FDA%20Draft%20Guidance%20-%20Collection%20of%20Race%20and%20Ethnicity%20Data%20in%20Clinical%20Trials%20and%20Clinical%20Studies%20for%20FDA-Regulated%20Medical%20Products%20Final%20(4%2029%2024).pdf

[2] 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 Netw Open.* 2021;4(2):e2037640. doi:10.1001/jamanetworkopen.2020.37640

[3] Loree JM, Anand S, Dasari A, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. *JAMA Oncol.* 2019;5(10):e191870. doi:10.1001/jamaoncol.2019.1870

[4] U.S. Census Bureau. 2023 National Population Projections Datasets. November 9, 2023. Accessed September 2024. https://www.census.gov/data/datasets/2023/demo/popproj/2023-popproj.html.

SPECIFIC COMMENTS

Attention to Racial and Ethnic Minorities

Throughout their lives, people of color experience discrimination, have poorer access to health care, and receive lower quality services than the general population. Starting in middle age, the toll of these experiences becomes evident. Among Black individuals, for example, that means more chronic medical conditions, which worsen over time, and in turn can contribute to increasing frailty and shorter lifespans. AGS recommends that the FDA align with the recently updated standards from the Office of Management and Budget (OMB)[5] that requires collection of detailed race and ethnicity data where possible unless it is determined that the potential benefit of the detailed data would not justify the additional burden or risk to confidentiality. We also encourage the FDA to expand on how sponsors can use this detailed data in analysis in appropriate ways.

Attention to Older Adults Including Better Attention to Older Age Subgroups

Considering the rapidly increasing size, diversity, and needs of the older population, more detailed demographic information will be crucial. A prior analysis of research found that 33 percent of federally funded clinical trials had an upper age limit, with one-quarter of the studies not allowing people 65 and older to participate.[6] Further, FDA reporting of adults 65 and older does not take into consideration the major changes in drug pharmacokinetics and pharmacodynamics that occur across the older age span—from 65 to very old ages (80 and older)—leading to underrepresentation of older adults who are very old in clinical trials.[7] AGS believes that guidance for more representative inclusion is especially important for those in older ages given the increasing prevalence of many diseases among the growing population of those older than 65. There may be a need to overenroll these groups (i.e., include sufficient numbers that may be greater than calculated by prevalence of the disease in that group in the trial to allow analyses). We recommend that age be reported with sufficient granularity to detect clinically important differences across and between older age subgroups (e.g., disaggregated data by age group such as <65, 65-70, 70-75, 80-85, and ≥85 years) as well as ensuring the inclusion of very old adults in clinical trials as part of the FDA's ongoing efforts to improve data when assessing the safety and efficacy of new drugs, products, and devices. The older population would be at greater risk for adverse effects and likely receive a large portion of such interventions, once approved.

Attention to Other Underrepresented Groups

AGS appreciates FDA's encouragement for research sponsors to consider additional demographic factors including but not limited to geographic location, gender identity, sexual orientation, socioeconomic status (SES), physical and mental disabilities, pregnancy status, lactation status, and co-morbidity considering the intersectionality of identities and the experience of multiple forms of discrimination across the life course. However, there is minimal guidance on how to use this data for the DAP. The COVID-19 pandemic demonstrated how the intersection of age, race, SES, and other factors contributes

[5] 89 Fed. Reg. 22182 (March 29, 2024)
[6] Lockett J, Sauma S, Radziszewska B, Bernard MA. Adequacy of inclusion of older adults in NIH-funded phase III clinical trials. *J Am Geriatr Soc.* 2019;67(2):218-222. doi:10.1111/jgs.15786
[7] Lau SWJ. History of FDA Guidance on Drug Evaluation in Older Adult Patients. Roadmap to 2030 for New Drug Evaluation in Older Adults Workshop; March 23, 2021. Accessed September 2024. https://www.fda.gov/media/147956/download

to poorer health outcomes for those of all ages in historically marginalized communities as exemplified by the finding that the location of one's neighborhood predicts survival from COVID-19.[8] Further, a multitude of studies show that the efficacy and effects of interventions can vary between populations.[9,10,11,12] It is vitally important to all of us that we take action to address these inequities. We recommend that FDA expand its guidance on collecting detailed sociodemographic factors beyond race, ethnicity, sex, and age in order to assess the level of diversity, equity, and inclusion and determine whether the evidence on drugs, products, and devices can be generalized to all underrepresented, disproportionately affected, or understudied populations.

Older adults with complex healthcare needs receive care in multiple care settings, including long-term care where much of the population disproportionately experiences multiple chronic conditions and polypharmacy. In the U.S., there are approximately 1.3 million residents in nursing homes[13] and more than 800,000 in assisted living communities.[14] Given that living environments have an impact on health, we believe consideration should be given to reporting whether clinical trial participants live independently in the community or facility settings. AGS strongly supports the inclusion of older adults in nursing homes, adult day centers, and other congregate living arrangements for increased trial enrollment and support for these underrepresented communities in clinical studies and trials.

Inclusion of Standardized Measures

Geriatrics health professionals provide care for older adults, usually over the age of 65, with complicated medical issues and social challenges. They focus on the 5Ms of geriatrics: **M**ultimorbidity, What **M**atters, **M**edication, **M**entation, and **M**obility.[15] Multimorbidity describes the older person who has more complex needs often due to multiple chronic conditions, frailty, and/or complex psychosocial needs. What Matters, Medication, Mentation, and Mobility describe the four main areas where geriatrics health professionals focus their clinical attention and form the basis for the age-friendly health systems framework that is focused on ensuring that all older people have access to this type of coordinated care,

[8] Hu J, Bartels CM, Rovin RA, Lamb LE, Kind AJH, Nerenz DR. Race, ethnicity, neighborhood characteristics, and in-hospital coronavirus disease-2019 mortality. *Med Care*. 2021;59(10):888-892. doi:10.1097/MLR.0000000000001624

[9] Ramamoorthy A, Pacanowski MA, Bull J, Zhang L. Racial/ethnic differences in drug disposition and response: review of recently approved drugs. *Clin Pharmacol Ther.* 2015;97(3):263-273. doi:10.1002/cpt.61

[10] Wang Y, Zhao X, Lin J, et al. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *JAMA.* 2016;316(1):70-78. doi:10.1001/jama.2016.8662

[11] MA BB, Hui EP, Mok TSK. Population-based differences in treatment outcome following anticancer drug therapies. *Lancet Oncol*. 2010;11(1):75-84. doi:10.1016/S1470-2045(09)70160-3

[12] Elahi M, Eshera N, Bambata N, et al. The Food and Drug Administration Office of Women's Health: impact of science on regulatory policy: an update. *Journal of Women's Health.* 2016;25(3):222-234. doi:10.1089/jwh.2015.5671

[13] Centers for Disease Control and Prevention. Nursing Home Care. November 5, 2023. Accessed September 2024. https://www.cdc.gov/nchs/fastats/nursing-home-care.htm

[14] American Health Care Association and the National Center for Assisted Living. Facts and Figures. Accessed September 2024. https://www.ahcancal.org/Assisted-Living/Facts-and-Figures/Pages/default.aspx

[15] Adapted by the American Geriatrics Society (AGS) with permission from "The public launch of the Geriatric 5Ms" [on-line] by F. Molnar and available from the Canadian Geriatrics Society (CGS) at The Canadian Geriatrics Society - Geriatric 5Ms. Accessed September 2024. https://thecanadiangeriatricssociety.wildapricot.org/Geriatric5Ms/

while also making sure personal needs, values, and preferences are at the heart of that care.[16] Cognitive function and physical function are especially significant to older adults as reflected in conceptual models for what matters most to older adults, such as the 5Ms,[17] and they are important considerations for investigating drugs, products, and devices. As an example, frailty is a substantial factor and predictor in clinical and primary outcomes that has shown to outperform other biological markers, which would help inform risk-benefit balance in clinical studies.[18]

Furthermore, chronic diseases related to aging, such as diabetes, heart disease, and cancer continue to afflict 80 percent of people 65 and older[19] and there is a high prevalence of polypharmacy in this population.[20] AGS recommends including consistent and standardized measures of multimorbidity (Elixhauser Comorbidity Index and Charlson Comorbidity Index), cognition (Mini-Cog™, Montreal Cognitive Assessment (MoCA)), function (Short Physical Performance Battery, Clinical Frailty Scale), and polypharmacy (at minimum, description of the number of drugs), at baseline which would greatly facilitate interpretation of study results and inform which are the most predictive of adverse outcomes or efficacy.

Setting Enrollment Targets

When determining diversity enrollment targets, as well as the comparator for U.S. clinical trial evaluations, AGS supports prevalence of disease-based enrollment targets for clinical trials, which is participation in proportion to the prevalence of the treatment indication or disease (i.e., Representative Participant Enrollment (RPE) in clinical trials).[21] For a trial population to be predictive of what will be observed post-marketing approval, the trial participants must reflect the eventual treatment population. FDA analyses for progress in enrollment of women have used a specific target of 0.8 – 1.2 for an "acceptable" participant to prevalence ratio. At the same time, it is critical to recognize that underrepresented groups may be underrepresented in prior studies that estimate disease prevalence. In light of this, AGS recommends careful consideration to obtaining comprehensive and inclusive estimates of disease prevalences in historically underserved and underrepresented communities and how this concern can be addressed.

We believe that a significant portion of the enrolled participants should be U.S. residents. There is a body of evidence showing that epigenetic or environmental, social, and lifestyle factors impact diseases

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[16] Institute for Healthcare Improvement. Age-Friendly Health Systems: Guide to Using the 4Ms in the Care of Older Adults in Hospitals and Ambulatory Care Practices. 2022. Accessed September 2024. https://forms.ihi.org/hubfs/IHIAgeFriendlyHealthSystems_GuidetoUsing4MsCare.pdf

[17] Tinetti M, Huang A, Molnar F. The geriatrics 5M's: A new way of communicating what we do. *J Am Geriatr Soc*. 2017;65(9):2115. doi:10.1111/jgs.14979

[18] Denkinger M, Knol W, Cherubini A, et al. Inclusion of functional measures and frailty in the development and evaluation of medicines for older adults. *Lancet Healthy Longev.* 2023;4(12):e724-e729. doi:10.1016/S2666-7568(23)00208-8

[19] National Prevention, Health Promotion, and Public Health Council. Healthy Aging in Action: Advancing the National Prevention Strategy. November 2016. Accessed September 2024. https://www.hhs.gov/sites/default/files/healthy-aging-in-action-final.pdf (Page 11)

[20] Delara M, Murray L, Jafari B, et al. Prevalence and factors associated with polypharmacy: a systematic review and meta-analysis. *BMC Geriatr*. 2022;22(601):1-12. doi:10.1186/s12877-022-03279-x

[21] Schwartz JB. An Initial Step to Improve Representativeness of Older Age Groups in Drug Development. Virtual Presentation at: Roadmap to 2030 for New Drug Evaluation in Older Adults Public Workshop: March 23, 2021. Accessed September 2024. https://www.fda.gov/media/147963/download

and responses to therapies.[22,23,24] Further, the medical practice differs as to the co-treatments patients would receive in different countries. It would be necessary to evaluate the efficacy and safety of a medication, device, or intervention in the target patient population, as well as under the conditions that the medication, device, or intervention will be ultimately used. As it is the responsibility of the FDA for U.S. approval and evaluation of clinical trials, we encourage the FDA to assure adequate enrollment of U.S. residents. Though it is difficult to ensure sufficient numbers to detect differences leading to different treatment, the approval decision should set a specific percentage for U.S. enrollment and FDA evaluations must include region and country comparisons. This recommendation is in line with a recent draft non-binding guidance issued by the FDA, ''Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs,"[25] which should be extended to evidence for more than oncology programs.

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Thank you for taking the time to review our feedback and recommendations. For additional information or if you have any questions, please do not hesitate to contact, Anna Kim at akim@americangeriatrics.org.

Sincerely,

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President

Nancy E. Lundebjerg, MPA
Chief Executive Officer

[22] Tiffon C. The impact of nutrition and environmental epigenetics on human health and disease. *Int J Mol Sci* 2018;19(11,3425):1-19. doi:10.3390/ijms19113425
[23] Ozomaro U, Wahlestedt C, Nemeroff CB. Personalized medicine in psychiatry: problems and promises. *BMC Medicine*. 2013;11(132):1-35. doi:10.1186/1741-7015-11-132
[24] Argentieri MA, Nagarajan S, Seddighzadeh B, Baccarelli AA, Shields AE. Epigenetic pathways in human disease: the impact of DNA methylation on stress-related pathogenesis and current challenges in biomarker development. *EBioMedicine*. 2017;18:327-350. doi:10.1016/j.ebiom.2017.03.044
[25] U.S. Food and Drug Administration. Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs Guidance for Industry, Draft Guidance. September 2024. Accessed September 2024. https://www.fda.gov/media/181824/download