

September 28, 2021

The Honorable Anna Eshoo
U.S. House of Representatives
Washington, DC 20515

Dear Representative Eshoo:

The American Geriatrics Society (AGS) greatly appreciates the opportunity to comment on the discussion draft of the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act. The AGS is a not-for-profit organization comprised of nearly 6,000 geriatrics health professionals who are devoted to improving the health, independence, and quality of life of all older adults. Our members include geriatricians, geriatrics nurse practitioners, social workers, family practitioners, physician assistants, pharmacists, and internists 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 patient care, research, professional and public education, and public policy.

We applaud your commitment and leadership to increase diversity in clinical trials and your efforts to ensure robust and equitable biomedical research. Inclusivity and representativeness are the core of rigorous research and development of safe and efficacious drugs, medical devices, and interventions for all populations. The lack of consideration for the appropriateness of target populations to whom drugs and devices are then marketed and provided to must be addressed. 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.

The AGS believes in a just society, one where we all are supported by and able to contribute to communities where ageism, ableism, classism, homophobia, racism, sexism, xenophobia, and other forms of bias and discrimination no longer impact healthcare access, quality, and outcomes for us all as we age. In order to achieve meaningful change in health care, the AGS leads efforts to ensure the evidence base that informs clinical care reflects diverse study populations.

We appreciate the opportunity to review this discussion draft and share our recommendations which we hope you will consider as you move through the legislative process.

GENERAL COMMENTS

One-Pager

The AGS recommends that the term, “demographic diversity” on the one-pager of the discussion draft, be defined to ensure clarity and understanding around the meaning and implications of the term. It would be helpful to understand the characteristics that would be included in the demographic data (e.g., race, gender, age, socioeconomic status, education).

The one-pager notes that there is currently no statutory requirement for diversity in study participants of clinical trials. **However, the AGS believes it would be important to acknowledge that there are efforts to try and address the lack of diversity in clinical trial participants.** At present, the National Institutes of Health (NIH) is mandated by the Public Health Service (PHS) Act to ensure women and minority populations are enrolled in studies – including subpopulations of minority groups¹ – and requires NIH-funded studies to report on the sex/gender and racial/ethnic composition of the study population.²

We also believe it is important to consider that though pharmaceutical trial sites may often be located at academic medical centers and not community health centers, it is not entirely true for all study sites.

Discussion Draft

The AGS appreciates the recognition that the COVID-19 vaccine trials lacked racial and ethnic diversity despite the disproportionate burden of the disease on underrepresented racial and ethnic minorities. We are also appreciative that the legislation requires the Secretary of Health and Human Services to submit a Congress report that includes consideration of how regulatory flexibilities to mitigate disruption of clinical trials during COVID-19 impacted certain patient populations' access to clinical studies and trials, particularly for underrepresented racial and ethnic minorities. However, it is crucial to recognize that the trials also lacked inclusion of nursing home residents.^{3,4} Older adults and nursing home and long-term care residents have been at substantially higher risk for serious complications and death due to COVID-19 compared with other population groups.^{5,6} **The AGS strongly supports the inclusion of nursing homes and adult day centers for community engagement and outreach to increase trial enrollment and support for underrepresented communities in clinical studies and trials.** Further, an additional barrier for older adults' participation in clinical trials – particularly for people who are socioeconomically disadvantaged – is the need for caregiver support to fully participate in the trial (e.g., transportation, documentation). Family caregivers may need to take time off from their jobs and formal caregivers are often paid hourly. **We encourage that attention be given to adequately funding clinical trials so that broader participation can be achieved.** NIH funding could also be directed to community engagement and outreach efforts to caregivers, family members, facility staff, and health care providers for older patients.

In addition, we support the proposed U.S. Food and Drug Administration (FDA) requirement on clinical trial enrollment and reporting for disaggregation of data by age group. At the same time, it would be important to not only disaggregate the data but analyze it with sufficient granularity to assess its relationship to prevalence. Currently, FDA reporting of adults 65 and older ignores the major changes

¹ See 42 U.S.C. § 289a-2.

² National Institutes of Health. Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. Available at <https://grants.nih.gov/policy/inclusion/women-and-minorities.htm>. Updated March 23, 2021.

³ Polack FP, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603–2615. <https://doi.org/10.1056/NEJMoa2034577>.

⁴ Baden LR, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403–416. <https://doi.org/10.1056/NEJMoa2035389>.

⁵ Centers for Disease Control and Prevention. People at Increased Risk: Older Adults. Available at <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html>. Updated July 3, 2021.

⁶ Centers for Disease Control and Prevention. People at Increased Risk: People Who Live in a Nursing Home or Long-Term Care Facility. Available at <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-in-nursing-homes.html>. Updated September 11, 2020.

in drug metabolism and responses 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 **The AGS believes that policy 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 – and recommends that age be reported meticulously to detect clinically important differences across and between older age subgroups, as well as the inclusion of very old adults in clinical trials who would likely receive a large portion of medications, once approved.**

The AGS is concerned that interventions that are not drugs or medical devices (e.g., prevention strategies, procedures, telemedicine) are not reflected in the legislation. There are not only clinical trials for drugs and devices under development but also interventions that are not a drug or medical device and would be vital to ensure diversity in the study population receiving these interventions so that research findings are generalizable to the target population. **Furthermore, the AGS encourages that the recruitment process be considered while working to advance diversity in research.** In order to achieve diverse enrollment in research studies, facilitating diverse recruitment would need to precede the enrollment.

We are also concerned about the ambiguous distinction between the FDA and NIH and believe that there needs to be more clarity to ensure that the legislation does not impair NIH research on interventions (i.e., non-pharmaceutical research), particularly in regions with low racial/ethnic diversity.

COMMENTS ON QUESTIONS

1. How can we best ensure sponsors are held accountable for enrolling participants that reflect the diversity of the intended patient population without inadvertently slowing research?

The AGS believes accountability would be best ensured through an enrollment analysis at an annual review of a sponsor’s trial and potential consequences of failing to meet ultimate enrollment targets. Funding for pilot programs could also allow investigation of the most successful ways to achieve representative and efficient enrollment and conduct of clinical trials. Other possibilities include establishing national networks, incorporating ongoing community-based research efforts (i.e., National Health and Nutrition Examination Survey (NHANES)) to gather a nationally representative database or research registry, and using health care chains or academic networks. Though other specialties have used incentives to reward successful enrollment or expanded patent protection times, we do not encourage this approach. It may instead be helpful to include inclusivity and representativeness as 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. Concomitantly, we believe attention must be given to ensuring this is balanced and does not unintentionally limit access to underinclusive parameters. **The AGS also supports the following significant steps to avoid inadvertent deceleration of research progress: (1) Adequately fund the infrastructure for research in communities; (2) Use pragmatic trials and less demanding or intensive research protocols; and (3) Embed research within our healthcare systems.**

⁷ Lau SWJ. History of FDA Guidance on Drug Evaluation in Older Adult Patients. Virtual Presentation at: Roadmap to 2030 for New Drug Evaluation in Older Adults Public Workshop: March 23, 2021. Available at <https://www.fda.gov/media/147956/download>.

2. How should diversity enrollment targets be determined? Should the targets be based on disease prevalence in the U.S.? How should international clinical trial data be considered?

When determining diversity enrollment targets, as well as the comparator for U.S. clinical trial evaluations, the 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).⁸ 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 a specific target of 0.8 – 1.2 for an “acceptable” participant to prevalence ratio.⁹ At the same time, it is critical to recognize that underrepresented groups are underrepresented in studies that estimate disease prevalence. In light of this, the AGS recommends the careful consideration of how this concern can be addressed.

The AGS also believes 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 and responses to therapies.^{10,11,12} 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 number for U.S. vs. international sites and FDA evaluations must include region and country comparisons.

3. How can we make post-marketing requirements more effective?

For greater effectiveness, the AGS encourages that the routine post-marketing safety monitoring duration to be extended to more than 18 months or at least 10,000 patient exposures. This will allow sufficient exposure for older adults as they are often not included in clinical trials nor are they within the first wave of patients prescribed medications that are not exclusively for older adults given safety concerns. **We recommend a similar timespan to ensure diversity since costs of newer therapies are often higher, local area coverage decisions can take time, people who are economically disadvantaged are often not adequately insured or on Medicaid, and newer drugs are not included in formularies or available in cost-controlled health care delivery systems.**

Additionally, the AGS supports accountability for manufacturers as part of post-marketing requirements when the FDA requires post-marketing studies. Without accountability, there would be no compliance.

⁸ 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. Available at <https://www.fda.gov/media/147963/download>.

⁹ Scott PE, et al. Participation of Women in Clinical Trials Supporting FDA Approvals of Cardiovascular Drugs. *Journal of the American College of Cardiology*. 2018;71(18):1960-9. <https://doi.org/10.1016/j.jacc.2018.02.070>.

¹⁰ Tiffon C. The Impact of Nutrition and Environmental Epigenetics on Human Health and Disease. *Int. J. Mol. Sci*. 2018;19(11):3425. <https://doi.org/10.3390/ijms19113425>.

¹¹ Ozomaro U, Wahlestedt, C & Nemeroff, CB. Personalized medicine in psychiatry: problems and promises. *BMC Medicine*. 2013;11(1):1-35. <https://doi.org/10.1186/1741-7015-11-132>.

¹² Argentieri MA, et al. 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. <https://doi.org/10.1016/j.ebiom.2017.03.044>.

We believe 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.

4. How should we structure grant programs within the Department of Health and Human Services to (1) enhance community engagement and outreach to underserved communities and (2) increase the capacity of Community Health Centers to participate in clinical trials and research?

One approach could be to require meaningful community engagement in any clinical trial application and collaboration with patients and/or caregivers in the planning, execution, and Data and Safety Monitoring Boards (DSMBs) as a condition for funding. By meaningful, we mean full partnership and engagement with patients, caregivers, and community-based organizations and clinicians. **The AGS also encourages sufficient funding so that community health centers engaged in initiatives to increase their capacity for clinical research can include outreach and engagement for nursing homes and adult day centers.** As noted above, diseases and treatment responses may be influenced by epigenetic factors. There are also working examples of successful community-based studies and networks, as well as examples targeted at racial minorities such as the Patient-Centered Outcomes Research Institute (PCORI) program – Addressing Disparities and Improving Healthcare Systems, focusing on comparing patient-centered approaches to improve the equitably, effectiveness, and efficiency of care¹³ – which can be expanded with partnerships or satellites within underserved community sites. Other examples that can be reinstituted or expanded include: [AGING Initiative](#), [IMPACT Collaboratory](#), [Framingham Heart Study](#), [Multi-Ethnic Study of Atherosclerosis \(MESA\)](#), [Atherosclerosis Risk in Communities \(ARIC\) Study](#), [Sacramento Area Latino Study on Aging \(SALSA\)](#), [San Antonio Heart Study \(SAHS\)](#), [Jackson Heart Study](#), [Multiple Risk Factor Intervention Trial \(MRFIT\)](#), [Cardiovascular Risk Development in Young Adults \(CARDIA\)](#), [Chicago Western Electric Study](#), and [Hispanic Community Health Study/Study of Latinos \(HCHS/SOL\)](#).

Furthermore, throughout the COVID-19 pandemic, we have seen that infrastructure for remote training and collaboration is possible. The AGS believes this should continue to be in place and utilized. **We also believe that to stimulate partnerships and involve organizations representing racial minorities in the design, recruitment, and operation of sites, funding for on-site training of partners and collaborative research would be essential as well as funding to ensure that people who are socioeconomically disadvantaged can participate.**

The AGS supports sustained funding for practice-based research networks or independent community health centers to facilitate and contribute to making referrals to trials. Community-based clinicians are trusted by their patients and funding must be provided to support the time it will take to educate their communities and to discuss participation in clinical trials with their patients. **In addition, AGS recommends that education about research as an important conduit to achieving better health outcomes must reflect the needs of underrepresented communities in order to build trust in research.**

¹³ Patient-Centered Outcomes Research Institute (PCORI). Healthcare Delivery and Disparities Research. Available at <https://www.pcori.org/about-us/our-programs/healthcare-delivery-and-disparities-research>. Published March 29, 2017.

Thank you for all you are doing to support diversity and equity in clinical trial participation. We appreciate the opportunity to submit these comments. For additional information or if you have any questions, please contact Anna Kim at akim@americangeriatrics.org.

Sincerely,

A handwritten signature in black ink that reads "Hollmann MD". The signature is written in a cursive, flowing style.

Peter Hollmann, MD
President

A handwritten signature in black ink that reads "Nancy E. Lundebjerg". The signature is written in a cursive, flowing style.

Nancy E. Lundebjerg, MPA
Chief Executive Officer