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June 30, 2017

Lisa Kaeser, JD
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
31 Center Drive, Room 2A03, MSC 2425
Bethesda, MD 20892-2425

RE: Invitation to Comment on Inclusion in Clinical Research Across the Lifespan (NOT-OD-17-059)

Dear Ms. Kaeser,

The American Geriatrics Society (AGS) is pleased to respond to the National Institutes of Health's (NIH's) Request for Information (RFI): Invitation to Comment on Inclusion in Clinical Research Across the Lifespan (NOT-OD-17-059).

The AGS is a not-for-profit organization comprised of nearly 6,000 geriatrics healthcare professionals and basic and clinical researchers specializing in aging. The AGS provides leadership to healthcare professionals, policy makers, and the public by implementing and advocating for programs in patient care, research, professional and public education, and public policy. Our vision for the future is that every older American will receive high quality person-centered care. In order to achieve this vision, we strive to help guide the development of public policies that support improved health and health care for older people.

In addition to our comments below that are specific to inclusion of older adults in clinical trials, we support the NIH ongoing efforts focused on inclusion of women and minorities in study populations. We believe that the best research is research that reflects the heterogeneity of America's population. We know that our colleagues in pediatrics will speak to the importance of ensuring that study populations reflect the opposite end of the life span and believe that these recommendations will be important as NIH looks at the ways in which it can support clinical trials that lead to improved health outcomes for all Americans, regardless of age, gender, or ethnicity.

We very much appreciated the opportunity to participate in the NIH's Inclusion Across the Lifespan Workshop held June 1-2, 2017. Multiple AGS members participated in the Workshop and helped us to develop our response to this RFI as follows:

General comments

Older adults, especially those with poor health, functional limitations and multiple chronic conditions, are frequently excluded from randomized clinical trials; however, these are the individuals who disproportionately suffer from many target conditions, generate a large share of healthcare costs, and who are most vulnerable to the adverse effects of medications and device-

based treatments. Despite these clinical realities, providers and older adults have little guidance on comparative effectiveness of treatments. We know that many drugs are more frequently prescribed to older adults despite the lack of inclusion in trials.[1]

We recommend that there be a stronger recommendation from NIH on the need for all clinical trials to actively enroll older adults—regardless of who is sponsoring the trial (e.g., NIH, industry). This will lead to a better understanding of the safety and effectiveness of drugs and other interventions for the patients who will increasingly be the ultimate recipients of these therapies. We believe that study populations should mirror the demographic prevalence of the conditions in the community—which translates into enrolling more, and more representative, older adults into trials.

Recommended terminology

The AGS strongly recommends that NIH establish a requirement that potential grantees use the terms "older adults" or "older people" when describing a study population that includes adults over the age of 65 and that NIH use this terminology in its RFAs and reports. This recommendation stems from our own work with the Frameworks Institute as a member of the Leaders of Aging Organizations (LAO). One key finding from this work is that older people report a negative reaction to terms like "seniors" and "the elderly" as these terms tend to "otherize" older adults. Specifically, such terms connote discrimination and negative stereotypes that undercut research-based recommendations for better serving our needs as we age. As detailed in an editorial published in the *Journal of the American Geriatrics Society* (*JAGS*), we will be requiring that authors use "older adults" or "older people" as opposed to "(the) aged," "elder(s)," "(the) elderly," and "seniors" when describing individuals aged 65 and older.[2]

Strategies that are successful to ensure all ages are included when appropriate

The AGS supports the following recommendations stemming from Workgroup 1 – Study Populations:

- Consent documents and strategies should accommodate/incorporate age, language, disabilities, mobility, and literacy of populations across the age span
- Targeted recruitment of an adequate number of older patients to ensure representativeness
- Individualized safety monitoring for people at higher risk for side effects
- Design studies for ease of participants rather than investigators
    - Enroll and follow up visits in or near participants' homes utilizing community health workers
    - Incentivize new technologies that promote ease of enrollment and follow up data collection (e.g., hearing and vision accommodations, literacy considerations, mobile units, transportation supports)
    - Support flexible methods of follow up (e.g., home visits, mobile units with research units, video technology)

[1] Bourgeois FT, Orenstein L, Ballakur S, Mandl KD, and Ioannidis JPA. Exclusion of Elderly People from Randomized Clinical Trials of Drugs for Ischemic Heart Disease. J Am Geriatr Soc 2017; doi:10.1111/jgs.14833
[2] Lundebjerg NE, Trucil DE, Hammond EC, Applegate WB. When It Comes to Older Adults, Language Matters: Journal of the American Geriatrics Society Adopts Modified American Medical Association Style. J Am Geriatr Soc 2017; doi:10.1111/jgs.14941

    - Pragmatic trials that leverage standard of care in clinical sites to promote enrollment when appropriate
- Make clinicians, patients, and families aware of clinical trials through targeted outreach as is appropriate for the study question through targeted professional communications and webinars, and materials in waiting rooms, exam rooms, EHRs, etc.
- NIH/institutional support to provide infrastructure for community engagement to assist recruitment of representative study populations
- Add "age" as a required category on the NIH enrollment table

These and other study recruitment and retention techniques and strategies to address concerns and overcome barriers to older adult participation in clinical research are detailed in an article by Dr. Lona Mody and colleagues.[3]

Strategies to expand current successful practices for inclusion of these populations

The AGS recommends that NIH provide guidance and incentives for investigators and organizations to explicitly plan an active enrollment strategy for older adults in the highest age strata and those with multiple chronic conditions.

The AGS also supports the following recommendations stemming from Workgroup 4 – Data Collection and Reporting:

- The peer review research evaluation process must have appropriate reviewer expertise to ensure inclusion and appropriate research designs for older adults
- Lack of expertise among Principal Investigators about older adult populations must be addressed; and experts in older populations and aging should be included on study teams, as appropriate

Age-related individual level data and/or summary statistics that could reasonably be provided as part of standard clinical trial reporting for NIH applicants, grantees, and clinicaltrials.gov reports

The AGS supports the following recommendations also stemming from Workgroup 1 – Study Populations:

- FDA regulations, industry, and federal government guidelines should require researchers to report by age, sex, race/ethnicity, and count or index of prevalent co-existing conditions
- Applicants should be required to justify age-based, comorbidity, or functional inclusion/exclusion with a strong scientific rationale
- Require investigators to inform NIH of and publish limitations in generalizing study results when the population does not adequately represent the population with the disease
- Require investigators to include a comparison of their planned/actual enrollment to epidemiological distributions of the target conditions by age, gender, race, and co-existing conditions
    - Encourage stratified enrollment to ensure adequate representation when appropriate

[3] Mody L, Miller DK, McGloin JM, et al. Recruitment and Retention of Older Adults in Aging Research. J Am Geriatr Soc 2008; 56:2340-2348.

- Require reporting by age categories and tracking of inclusion older persons in NIH-sponsored clinical trials to inform next-steps

Metrics that would be most helpful for the interpretation of clinical study results – specific age groups, mean age with SD, median age with SD, or some other metric

The AGS supports the following recommendations stemming from Workgroup 2 – Study Designs and Metrics and Workgroup 4 – Data Collection and Reporting:

- Purposeful recruitment of older, sicker adults to better match and represent the population being studied
    - Once an adequate sample is achieved, close out age groupings and redirect recruitment efforts to remaining age groups
- Make NIH-funded clinical trials data, and applicable biospecimens, if any, be publicly and quickly available for analyses. Such data should either include age (if reported at the individual level), or be stratified by age (if group level data) to facilitate subgroup meta-analysis.
- Maintain real-time metrics on the inclusion of older adults as a top priority
- Harmonize the age reporting structure across NIH, ClinicalTrials.gov, and journals
- Studies should not only indicate the overall age range of the study population, but more importantly, how many people within each age group were included. We suggest collecting the age strata below and to enforce these categories for ClinicalTrials.gov as a first step.
    - 0 – 28 days
    - 29 days – 364 days
    - 1 – 5 years
    - 6 – 12 years
    - 13 – 15 years
    - 16 – 18 years
    - 19 – 21 years
    - 22 – 25 years
    - Starting at age 26, 10 year increments up to 65 years
    - 65+ in five year increments
- Assess inclusivity with a Trans-NIH evaluation comparing anticipated enrollment in the application versus actual enrollment versus published enrollment

Approaches to standardized reporting of age-related enrollment, data analysis issues, and results that would be most helpful to moving science forward

The AGS supports the following recommendations stemming from Workgroup 2 – Study Designs and Metrics:

- Encourage more pragmatic trials that are generalizable to the at-risk population
    - Stress multivariable, risk-based analytic methods to include all subjects
- Consider adaptive trials[4,5,6] (i.e., sequential, multiple assignment, randomized trials) and platform trials[7,8] with flexible features such as dropping treatments for futility, declaring one

[4] Almirall D, Compton SN, Rynn MA, Walkup JT, Murphy SA. SMARTer discontinuation trial designs for developing an adaptive treatment strategy. J Child Adolesc Psychopharmacol 2012;22:364-74.

or more treatments superior, or adding new treatments to be tested during the course of a trial
- Consider preference and other designs for non-drug interventions
- Make greater use of observational data to expand information for under-represented populations (i.e., meta-analytic methods, causal inference methods)
- Develop a standard template for listing age and important age-associated conditions (e.g. function) in Table 1 to be used across journal articles

Inclusion/exclusion criteria that might facilitate enrollment of pediatric and older populations in clinical trials

The AGS recommends that the "default" on Grants.gov and NIH enrollment tables be "no upper age exclusion." NIH should accompany this with grant review criteria and scoring relevant to the active inclusion of the relevant study population (i.e., those most burdened with the illness in question).

The AGS also suggests that FDA exemption of older populations for additional trials not only be based on age, but also factor in multiple chronic conditions, functional limitations, and cognitive difficulties. Similar to pediatrics, FDA should be able to request fast tracking of older adult trials if Phase II results are positive and sufficient data support these findings.

Any other concerns that NIH should consider in the recruitment of pediatric and older adult populations into clinical studies

The AGS supports the following recommendations stemming from Workgroup 1 – Study Populations and Workgroup 4 – Data Collection and Reporting:

- Address the balance of efficacy versus effectiveness
- Ensure that the inclusion of older adults is meaningful. In some instances, trials should just focus on older adults (e.g., statins for primary prevention).

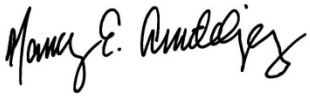
* * * * * *

[5] Collins LM, Murphy SA, Strecher V. The multiphase optimization strategy (MOST) and the sequential multiple assignment randomized trial (SMART): new methods for more potent eHealth interventions. Am J Prev Med 2007;32:S112-8.
[6] Kelleher SA, Dorfman CS, Plumb Vilardaga JC, et al. Optimizing delivery of a behavioral pain intervention in cancer patients using a sequential multiple assignment randomized trial SMART. Contemp Clin Trials. 2017;57:51-57.
[7] Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. JAMA 2015;28;313:1619-20.
[8] Bateman RJ, Benzinger TL, Berry S, et al. The DIAN-TU Next Generation Alzheimer's prevention trial: Adaptive design and disease progression model. Alzheimers Dement 2017;13:8-19.

Thank you for the opportunity to submit these comments. We would be pleased to answer any questions you may have. Please contact Anna Mikhailovich, amikhailovich@americangeriatrics.org.

Sincerely,

Debra Saliba, MD, MPH, AGSF
President



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