

VIEWPOINT

Inclusion Across the Lifespan NIH Policy for Clinical Research

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In 2005, a trial supported by the National Institutes of Health (NIH) that included patients with a mean age of 60 years demonstrated that implantable cardioverter-defibrillators had improved survival rates over amiodarone in patients with congestive heart failure.¹ This study and another that examined cardioverter-defibrillator therapy contributed to change in clinical practice.² However, 40% of patients who subsequently received cardioverter-defibrillators were older than 70 years and 10% to 20% were older than 80 years,² illustrating the importance of adequate inclusion of appropriate populations in clinical studies. In a review of 109 clinical trials, Zulman et al found inadequate inclusion of older adults to allow for informed decision making.³ In a review of 338 phase 3 and phase 4 NIH-funded studies that were actively recruiting in ClinicalTrials.gov, Spong and Bianchi noted that 75.7% explicitly excluded children, contributing to problems with adequate information for pediatric dosing and other interventions.⁴

To help reduce inadequate inclusion of younger and older populations, the NIH's Inclusion Across the Lifespan (IAL) policy⁵ will become effective for all grant applications submitted on or after January 25, 2019. This

by sex/gender and race/ethnicity could be performed. In 1998, the NIH issued a policy regarding the inclusion of children in clinical research and amended the policy in 2015 to clarify the definition of a child as someone younger than 18 years.⁷

With the passage of the 21st Century Cures Act in December 2016,⁸ Congress required the NIH to collect data on the inclusion of participants in clinical trials by age. Congress also required the NIH to (1) convene within 180 days a workshop on age groupings and age exclusions in clinical research, (2) post workshop findings on an NIH website, (3) publish data on age of participants in NIH-funded clinical research, including pediatric subgroups, and (4) determine, within 180 days of the workshop, whether to revise inclusion guidelines on age.

IAL Workshop

The NIH convened the workshop in June 2017 to consider issues of the inclusion of infants, children, adolescents, and older adults in clinical studies. Experts in pediatrics, geriatrics, biostatistics, ethics, and scientific publication were assembled for the workshop. The NIH charged the group to consider opportunities for enhanced participation of these populations regardless of whether the research was funded by the NIH.

The participants of the workshop identified opportunities for enhancing the inclusion of pediatric and older populations.⁹ Some suggested changes that could be implemented in the short-term included reviewing and revising NIH policies on the inclusion of pediatric and older adult populations to maximize in-

clusiveness; revising grant applications to ensure inclusion; reinforcing to reviewers that inclusion is part of the review criteria; and reporting by age and tracking inclusion of children and older adults in clinical studies.⁹

Subsequent Actions

Extensive discussion at the workshop focused on the need for more detailed information regarding the age of individuals participating in clinical research and the challenge of appropriately representing age. Age might be categorized in one way for one research question, and in another way for a different question. Given the choice, many researchers prefer using continuous rather than categorical data because more can be learned from analyses presented in different ways. For example, for a study participant who is 12 years old and another participant who is 8 years old, more granular information can be obtained from analyses that consider the participant's individual age, rather than from

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policy is the next step in a series of policies to facilitate the inclusion of scientifically appropriate and relevant populations for the many questions addressed by NIH-funded clinical researchers. In this Viewpoint, we summarize the policies and mandated activities that preceded the IAL policy and the provisions of the policy. The implementation of this policy will have implications for all clinical research supported by the NIH and should enhance transparency and support reproducibility of clinical study findings in broader populations.

Inclusion Policy History

Following NIH guidance on inclusion of women in clinical studies in 1986, the NIH developed a policy responsive to legislation requiring inclusion of women and minorities in NIH-funded clinical research in 1994.⁶ This policy included a requirement that phase 3 clinical trials subject to US Food and Drug Administration regulation be designed such that a valid analysis stratified

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Figure. Summary of the National Institutes of Health's (NIH's) Inclusion Across the Lifespan Policy

NIH Inclusion Across the Lifespan Policy
<p>► Include an inclusion plan in grant applications or proposals.</p> <p>Submit a plan for including individuals across the lifespan in clinical research.</p> <p>If excluding based on age, provide rationale and justification for the specific age range.</p> <p>Scientific Review Groups will assess each application or proposal as being acceptable or unacceptable with regard to the age-appropriate inclusion or exclusion of individuals in the research project.</p>
<p>► Report participant age at enrollment in progress reports.</p> <p>Participant age at enrollment, sex or gender, race, and ethnicity data must be included in progress reports.</p> <p>Age at enrollment may be reported to NIH in units ranging from hours to years.</p>

analyses that include the 12-year-old child in a group defined as "aged 12 to 18 years" and the 8-year-old child in a group defined as "aged 6 to 11 years." Therefore, the NIH will ask investigators to submit anonymized individual-level data on age and other demographics. These data will make it possible for the agency to answer questions such as "What are the sex-specific age distributions of men and women enrolled in NIH-funded studies of Paget disease of bone?" Going forward, this change will allow the NIH to respond to another provision of the 21st Century Cures Act that calls for reporting of demographics of participants of NIH-funded studies by disease category.

The IAL policy, summarized in the Figure, calls for researchers to justify a higher or lower age requirement for participation in clinical

studies. The policy also calls for grant application reviewers to carefully consider the age groups proposed for studies to determine whether the projected population is appropriate for the scientific question being posed.

Challenges

Enrolling older patients in clinical trials invariably means patients with more comorbidities will be included in studies, meaning that the data will be "noisier." This inclusion of older patients and the identification of heterogeneity of treatment response among subgroups (eg, very old, very young) may, in some cases, impose the need for larger sample sizes. But, the inclusion of potentially more heterogeneous groups of older and younger patients also challenges investigators to identify more nimble, cost-effective approaches (eg, adaptive or Bayesian designs).⁹ Researchers will need to consider better ways to collect data to efficiently facilitate the conduct of larger-scale trials at a reasonable cost, such as through randomized registry trials. In addition, there will be a need for a cultural challenge to make it acceptable to enroll more complex patients into trials.

Expected Outcomes

The IAL policy, and the review and reporting requirements associated with it, should help ensure that children and older adults are not inappropriately excluded from clinical studies. The policy also has the potential to provide a more robust understanding of the full spectrum of participants recruited into clinical studies. Insights garnered from this expanded inclusion approach could enhance reproducibility and generalizability of clinical study findings.

ARTICLE INFORMATION

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