COMMENTARY

"Unjustified Partiality or Impartial Bias? Reckoning with Age and Disability Discrimination in Cancer Clinical Trials"

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In this issue, Zakout discusses European Union (EU) legal provisions for inclusion of patients of all types in clinical trials.[1] Shee highlights the unfortunate failure to include adequate numbers of older adults and adults with disabilities in clinical trials of anti-cancer agents. We agree with her argument that this is an ethical issue as well as a scientific and clinical issue.

We provide a US perspective as evaluation of new therapies is a universal issue and exclusion of subpopulations of patients in clinical trials may harm patients worldwide. Patients excluded from clinical trials of therapeutic agents often receive the agent after regulatory approval, though both the efficacy and adverse effects of the agent may be very different in them. The goal of having clinical trial participants be representative of populations likely to be eventual users of new therapeutic agents is frequently stated.[2] Over the past 35 years, the FDA has issued repeated guidances emphasizing the need for enrollment of older persons in clinical trials.[3] However, as noted by Zakout and others,[4] enrollment of sufficient numbers of older adults has not happened. We believe this failure is because prior guidances are not binding on the FDA or study sponsors and lack penalties.

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It is time for this to change. The pivotal Consolidated Appropriations Act, 2023 includes the Food and Drug Omnibus Reform Act (FDORA) that provides binding legal requirements for achieving clinically representative enrollment of adults in trials of new therapies tested in pivotal trials conducted for marketing approval.[5] It requires a diversity action plan (DAP) for clinical studies be submitted no later than the time of submission of plans for Phase 3 clinical studies as part of an Investigational New Drug application. Goals should be based on age group, sex, racial, and ethnic demographics of clinically relevant study populations, ideally based on estimated prevalence or incidence in the US of the disease or condition. Additional representation goals may include geographic location (metropolitan, rural), socioeconomic status, and non-demographic factors including comorbidities. Exclusion criteria must be justified, in contrast to EU legislation[6] and importantly, annual clinical trial reporting on enrollment must be submitted to FDA for review. FDORA also requires that FDA annually submit to Congress, and publish on the Agency's website, a report that summarizes in aggregate the DAPs received and whether clinical studies conducted met the demographic enrollment goals from the submitted DAP. As drug evaluation is now an international endeavor, the law should change the clinical trial landscape.

Implementation will need consensus on key issues such as how to define and evaluate representativeness and definitions for medical and health-related conditions and comorbidities. Age representativeness requires including patients across the spectrum of old age. The common practice of dichotomizing age as above or below 65 years is inadequate. Granular age-stratified prevalence data and trial enrollment data

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are essential. Trial enrollment should be evaluated for age-proportional representation by 5-or 10-year increments. The participant to patient ratio (PPR) defined as the ratio of the percentage of a group among clinical trial participants to the percentage of patients in that group among the US prevalent population is a logical measure. It has been used to assess representativeness of age or sex in clinical trials of FDA-approved medications.[7]

Adequate representation of older persons, however, involves much more than chronologic age considerations. Older persons of similar age vary greatly in health characteristics such as extent of comorbidity, functional impairment, frailty, polypharmacy, prevalence of geriatric syndromes such as falls, incontinence, and sensory impairment. These factors can greatly impact the effectiveness and side effects of therapeutics. The absence of data on these factors in clinical trials makes therapeutic choices in older patients very difficult.

A potential pitfall of PPR analyses is that only the "healthiest in the age group" may be enrolled. Sufficient numbers of those at greatest risk for adverse outcomes may not be enrolled and subgroups enrolled may be insufficient for comparative efficacy and safety analyses. Measurement or evaluation of representativeness for conditions will need standardized definitions. As Zakout notes,[8] there is no standardized definition for "disability." Yet there are standardized definitions for functional abilities[9] that may be a preferable consideration than "disability." Alterations in function may be highly important to people and may be especially affected in older adults by drugs with effects on the central nervous system. It is important that gold standard or preferred measures for functional abilities, and non-International Classification of Diseases coded disorders highly prevalent in older adults, be incorporated into evaluations of "representative" enrollment.

FDORA required FDA to publish binding guidance for implementing the requirements. Draft guidance published in June, 2024 addresses Diversity Enrollment Plans (DAPs).[10] Plans must include goals for enrollment disaggregated by race, ethnicity, sex, and age of clinically relevant demographic characteristics of the clinically relevant population. A rationale for goals must be included and generally, enrollment goals should be informed by the estimated prevalence and distribution of the disease or condition in the US intended use population. An explanation of how the sponsor intends to meet such goals must be provided. DAPs should apply to the entire study and enroll a population representative of the US intended use population whether conducted internationally or not. Descriptors of race and ethnicity and disease distribution are not uniform across the globe and may present challenges. FDA may grant a full or partial waiver from requirements but given the importance of increasing enrollment of historically underrepresented populations in clinical studies of drugs and devices, full or partial waivers will be rare.

"[E]xclusion" of subpopulations of patients in clinical trials is a universal issue. Older adults are the major consumers of medications. Inclusion of older adults representing patients likely to receive a medication must be included in clinical trials to determine the efficacy and safety in these patients. We agree with Zakout that there is both a scientific and ethical mandate for their inclusion.

The legislation also includes a requirement for annual reporting for "accountability." What the FDA draft guidance does not address is how it will determine inadequacy of submitted clinical trial plans, or what responses will be made to annual reporting, or what penalties might ensue. The ultimate success of the legislation on improving representative enrollment in clinical trials will depend on these factors.

In closing, exclusion of subpopulations of patients in clinical trials is a universal issue. Older adults are the major consumers of medications. Inclusion of older adults representing patients likely to receive a medication must be included in clinical trials to determine the efficacy and safety in these patients. We agree with Zakout[11] that there is both a scientific and ethical mandate for their inclusion. Approval for marketing of new medical therapies is performed by multiple agencies around the world and current legislation or guidance for drug approval therefore differs despite attempts for harmonization. We hope that recent changes in US legislation to require clinical trials for evaluation of new therapies for marketing to enroll representative clinical trial participants is a major first step in addressing current inequalities.

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Note

The authors have no conflicts to disclose. All disclosure forms are on file with the Journal.

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