Representative enrolment of older adults in clinical trials: the time is now

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Older adults (ie, those aged 65 years and older) represent about 17% of the US population and are responsible for about 34% of all prescription medication use. Nearly nine in ten older adults report taking at least one prescription medicine.[1] Agencies responsible for marketing approval of medications, academic societies, national and international organisations, health professionals, research funding entities, journals, and patient advocacy groups have long recommended that new medications should be evaluated in patient groups representative of the clinical population of the disease or condition that will be treated.[2–5] With the exception of medications for diseases that occur predominantly with older age, older adults have been under-represented in clinical trials of medications that they are likely to receive. [6]

In the USA, major gaps in clinical trial participation during new drug evaluation include: insufficient enrollment of (1) those aged 75 years and older, especially those older than 80 years, (2) those with multimorbidity (ie, more than 3 chronic conditions), (3) those receiving polypharmacy (ie, three or more regular medications), and (4) those with a state of increased vulnerability across multiple health domains that leads to adverse health outcomes. An absence of accepted criteria for a representative population for clinical trial enrolment has also been identified.[7] The consequence is that prescribers do not have the information needed to appropriately prescribe many new medications for older adults when drugs become available for clinical use. Efficacy could be lower and side effects higher in real-world older populations than reported from pivotal clinical trials of medications.

Potential solutions suggested to close this gap are the elimination of unnecessary eligibility criteria, removing barriers such as transportation and complex trial design and participation burden, improving perceptions of and access to drug evaluation research, addressing ethical concerns, expanding relevant research efforts to long-term care and assisted living populations, and developing universal definitions for conditions that affect older adults, the measurement of these conditions, and relevant terminology.[7] However, perhaps the most important solution is to establish clinical trial enrolment goals based on the prevalence of disease or disorder in the target treatment population.[7] None of these observations or recommendations are new, suggesting that recommendations will not be enough.

Recent attention in the USA has focused on inequities in the health care of subgroups of the population. The COVID-19 pandemic brought a focus on the disproportional burden and death rates of minoritised groups and older adults. Extreme under-representation of minorities and older adults in trials of COVID-19 vaccines and therapies was also publicised.[8,9] These events created an environment conducive to passing legislation by the US Congress to improve the conduct of clinical trials.

Such legislation was included in The Consolidated Appropriations Act of 2023,[10] passed in December, 2022. Within the Act, so-called cross-cutting provisions included requirements and accountability for clinical trial diversity and modernisation (panel). This Act provides the US Food and Drug Administration (FDA) with a legal mandate for additions to the requirements for clinical trials.

The first of these additional requirements is that of a require diversity action plan for phase 3 clinical studies or equivalent pivotal trials. Sponsors must submit a diversity action plan for review before or at the time of initial protocol submission to the FDA. The plan must specify goals by age group, which can be based on the estimated prevalence or incidence in the USA of the disease or condition for which the drug or device is being investigated, and characteristics of the target patient population, which could include demographic and non-demographic factors, including comorbidities.

The second new requirement is for the FDA to hold public workshops within 1 year from Act implementation for stakeholder input on four key points: (1) increasing enrolment of historically under-represented populations, (2) encouraging participation that reflects the disease or condition prevalence among demographic subgroups, (3) how and when to collect and present prevalence or incidence data by demographic subgroup, and (4) establishing enrolment goals, including the relevance

Panel: Summary on clinical trial diversity of the cross-cutting provisions of the US Consolidated Appropriations Act of 2023

SEC. 3601: diversity action plans for clinical studies

For a new drug that is a phase 3 study or, as appropriate, another pivotal study of a new drug (other than bioavailability or bioequivalence studies), the sponsor is required to submit a diversity action plan that includes:

- Goals for enrollment
- Rationale for such goals and
- Explanation of how the sponsor intends to meet such goals

SEC. 3602: guidance on diversity action plans-due within 2 years

The Secretary shall update or issue guidance for clinical study enrollment disaggregated by age group, sex, racial and ethnic demographics of clinically relevant study populations and may include characteristics such as geographic location and socioeconomic status, including the rationale for the sponsor's enrollment goals, which may include:

- estimated prevalence or incidence in the U.S. of the disease or condition for which the drug or device is being investigated if such estimated prevalence or incidence is known or can be determined based on available data;
- what is known about the patient population including, if available—demographics, which may include age group, sex, race, geographic location, socioeconomic status, and ethnicity
- non-demographic factors, including co-morbidities
- potential barriers to enrollment, such as patient population size, geographic location, and socioeconomic status;
- any other data or information relevant to selecting appropriate enrollment goals, disaggregated by demographic subgroup

SEC. 3603: public workshops—due within a year

The FDA must hold one or more public workshops to solicit input from stakeholders on increasing enrollment of historically underrepresented populations in clinical studies and encouraging clinical study participation that reflects the prevalence of the disease or condition among demographic subgroups, where appropriate, and other topics, including:

- how and when to collect and present the prevalence/incidence data on a disease or condition by demographic subgroup
- establishment of goals for enrollment in clinical trials, including the relevance of the estimated prevalence or incidence, as applicable, in the U.S of the disease or condition for which the drug or device is being developed; and

SEC. 3604: annual summary report on progress

Beginning not later than 2 years after the date of enactment of this Act (December 2022), and each year thereafter, the Secretary shall submit to the Congress, and publish on the public website of the Food and Drug Administration, a report that:

- summarizes, in aggregate, the diversity action plans received; and
- contains information, in the aggregate, on (A) whether the clinical studies conducted with respect to such applications met the demographic subgroup enrollment goals from the diversity action plan submitted for such applications; and (B) the reasons provided, if any, for why enrollment goals from submitted diversity action plans were not met.

This panel contains text that is a condensed version of the original wording of the US Consolidated Appropriations Act of 2023.

of estimated prevalence or incidence in the USA of the disease or condition for which the drug or device is being developed.

The third new requirement the Act brought was for the development of new guidance, as the FDA must publish guidance for diversity action plans for clinical trials within 2 years from the Act's implementation.

The final requirement is for accountability. Sponsors must report annually on diversity enrolment and the FDA must provide annual summary reports to Congress and publish aggregate data on the FDA public website about diversity in clinical studies beginning within 2 years from the Act's implementation.

For the first time, the USA has legal requirements to ensure the adequate representation of older adults and other traditionally under-represented populations in clinical trials. The upcoming years provide the opportunity for input on the final guidance and requirements of sponsors to achieve the goal of evaluating new drugs in the populations likely to receive them. The Act is also a call to other agencies and countries to match this effort. New medications can only be used most effectively in the clinical setting if the information regarding the safety and efficacy in patients who are likely to receive them is gathered during the drug evaluation process. The USA has taken much needed and long overdue legal action to ensure this goal is reached.

We declare no competing interests.

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