

Older Adults in Clinical Research and Drug Development Closing the Geriatric Gap

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*“For age is opportunity no less
Than youth itself, though in another dress,
And as the evening twilight fades away
The sky is filled with stars, invisible by day.”*

—Henry Wadsworth Longfellow

As cardiovascular specialists, we are caring for a rapidly growing number of older adults despite limited data to guide therapeutics in this population. During the next 25 years, the population age ≥ 85 years will be more than double—from 6.3 million in 2015 to 14.1 million by 2040.¹ Over 25 years ago, the Food and Drug Administration (FDA) published the *Guideline for the Study of Drugs Likely to be Used in the Elderly* advocating that the population studied should reflect the population treated.² A 2011 review by Cherubini et al³ demonstrated that 25% of heart failure trials had an arbitrary upper age exclusion; in the same year Zulman et al⁴ demonstrated that 45.6% of trials had other criteria that disproportionately excluded older adults (eg, decreased life expectancy, functional limitations, cognitive impairment, serious concomitant illness, or nursing home residence). Furthermore, many trials underrepresent women, who comprise the majority of older cohorts. Thus, it is no surprise that Medicare beneficiaries, almost all of whom have multiple chronic conditions, differ significantly from participants in trials used to inform Medicare coverage decisions.⁵ The application of data and treatment recommendations from studied to unstudied populations can result in catastrophic consequences and increased costs. The medical community has suggested elimination of age-based exclusions, justification for exclusion criteria that limit inclusion of older individuals, performance of trials specific to older individuals, and reporting trends to assess inclusion of older adults in clinical trials.⁶ However, as a medical community, we have yet to embark on the kind of systematic effort necessary to ensure representation of older adults in pivotal research.

Policy Efforts

There has also been slow bureaucratic progress. In 2012, the FDA published the *ICH-E7 Studies in Support of Special Populations: Geriatrics Guidance for Industry*, which presented nonbinding recommendations to improve representation of

older adults in trials.⁷ This document reiterated the importance of including older adults in research, encouraged early discussions with FDA, and outlined similar suggestions to those made previously.⁶ In 2014, the FDA prepared an action plan to Section 907 of the Food and Drug Administration Safety and Innovation Act (Pub L. 112–144) in which Congress directed them to report safety and effectiveness by sex, age, race, and ethnicity.⁸ The *FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data*, included the creation of Trial Snapshots for FDA-approved products to provide a subgroup summary for consumers.⁹ The geriatric population is considered to be those aged 65 years and older. Among the initial FDA Trial Snapshots is one for Vorapaxar (Zontivity), a thrombin receptor antagonist. Vorapaxar, when given in addition to antiplatelet therapy to patients with cardiovascular disease, led to a minor reduction in cardiovascular outcomes, but increased bleeding. A black box warning advises against use in those with previous stroke or bleeding. The snapshot states no difference was noted by patient age, but only 17% of the definitive trial, and 9% of the overall drug experience was collected in those aged >75 years.¹⁰ Paradoxically the package insert also states that older patients are at higher risk of bleeding which should be considered before initiating Zontivity.¹¹ Although age ≥ 65 years is a convenient cut point for clinical trial populations, age ≥ 75 years better reflects older adults in the community, and age ≥ 85 years is arguably the most reflective of a vulnerable age-defined cohort. Yet, cut points are numeric constructs. More relevant for benchmarking inclusion of representative older adults is their similarity to those likely to be treated. The well-intentioned consumer FDA snapshots are also profoundly limited by the continued lack of inclusion of older representative adults on which to base their information.

Approaches in Other Special Populations

The systematic path to better evidence in older adults may be informed by progress in other special populations. These examples of regulated approaches are actionable for older adults. First, targeted/planned enrollment tables required for sex/race/ethnicity in National Institutes of Health trials could serve as a model for required enrollment plans for

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older adults in National Institutes of Health clinical research. Research in support of new drug or device applications to the FDA, which may proceed to commercial use in older adults, should similarly include plans to ensure adequate enrollment of older adults. This would start the conversation early enough in planning to set target numbers of older adults and collect outcomes of relevance to them. Second, Congress could create an Office of Geriatric Health and Aging within the FDA to review protocols for dosing, enrollment, and data collection in older populations. This office could also monitor progress in the inclusion of older adults in pivotal trials. The FDA has dedicated offices for other special populations, such as the Office of Women's Health, Office of Minority Health, and Office of Pediatric Therapeutics. The FDA Office of Women's Health was created by Congressional mandate in 1994 and was associated with substantial improvement in recruitment of women. From 1988 to 1991, 47% of new drug applications analyzed the clinical trial data for sex differences, whereas from 1998 to 2000 these sex-specific analyses increased to ~70%.¹² However, no advisory committee or dedicated office exists for older adults to oversee or advocate for their representation. Third, the Pediatric Exclusivity Rule (1997) provides drug manufacturers a 6-month patent extension for conducting studies in children. From 1998 to 2012 of drugs given such patent extensions, 173 drugs (92%) received new pediatric labeling as a result of targeted studies in children.¹³ The Pediatric Exclusivity Rule came about through an act of Congress; a similar act should be passed to protect our citizens at the other end of the age spectrum. Both have unique aspects of their physiology, which may alter pharmacokinetics and pharmacodynamics. The analogous Geriatric Exclusivity Rule would build on lessons learned in pediatrics to optimize the economics, feasibility, and compliance with this policy initiative and capitalize on methods for mining data from registries and electronic records.¹⁴ Moreover, although device approval within the FDA often mandates postmarketing registries, the FDA should similarly approve drugs contingent on accumulation of postmarketing safety data in community-treated older adults. Fourth, a geriatric evidence rating in the package insert could provide a simplified uniform risk/benefit score. The Pregnancy Rating Category on labels indicates safety during pregnancy and summarizes strength of evidence for harm. A similar initiative could be used to integrate strength of evidence for risk-to-benefit of a drug in older adults. The analogous Geriatric Rating Category could provide an easy reference for those considering treatment, with highest rating for drugs tested in representative populations with information on comorbidity, function, drug interactions, and quality of life. This could also provide an incentive for pharmaceutical companies to test medications in older adults to distinguish them from in-class competitors by improving their Geriatric Rating.

Engage Patients and Other Stakeholders

Perhaps the best hope for closing the geriatric gap is including consumers, payers, and older adults in the discussion. Our elders, many of whom are eager to connect and contribute to future generations, need education and encouragement to understand participation in clinical trials. Simplified consent

forms with large type, added time to consult with family, the use of proxy data or remote follow up, and other ideas can be elicited to overcome barriers to participation. Payers, including Medicare, could provide education about the importance of research participation in subscriber welcome packets, creating a special identifier for those willing to be contacted for participation. This could spark community wide conversations among older adults about their role as research participants and rights as healthcare consumers. The FDA Office of Women's Health held regular public webinars in 2015 with stakeholder groups to gather feedback on the pregnancy and lactation labeling changes; if there were an office dedicated to older adults at FDA, similar discussions might occur with respect to labeling changes for older adults.¹⁵ One shining example of progress was the Multimorbidity in Cardiovascular Disease Conference. In February 2015, the National Institute on Aging, American Geriatrics Society and American College of Cardiology cohosted this workshop at which stakeholders from industry, patient representatives, researchers, and medical authorities met to propose solutions to the challenges of studying complex older populations. Similarly, payers should partner with drug and device manufacturers to identify research priorities for older populations and collaborate in research designs. Drugs and devices with best evidence would be given market advantage by payers, a benefit passed on to older adults through safer care at lower costs. When consumers exercise their full power, the drug and device industry will be motivated to gather this information, regardless of enhanced regulations or advocacy offices.

Conclusions

Continuing to describe but not close this geriatric gap for another 25 years will send health care for older adults blindly over the demographic cliff ahead. Despite concerns about implementation, cost, and political hurdles, we can learn from progress made for other special populations. It is time to act—we must design and implement mandates, partnerships, and incentives to ensure representation of older adults in the evidence which forms the basis of their care.

Disclosures

None.

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