# Inclusion of Older Adults in Research: Ensuring Relevance, Feasibility, and Rigor

*This Editorial comments on the articles by Vaughan et al, Bowling et al, and Lockett et al. in this issue.*

## MAJOR PROGRESS TOWARD INCLUSION OF OLDER ADULTS IN RESEARCH

The success and impact of all human subject research depends on the ability of investigators to recruit and retain suitable research volunteers. Moreover, if research findings are to inform clinical practice, then study participants must appropriately reflect the population being considered. Few would argue that children are merely smaller versions of 30-year-olds or that men and women should be viewed through the same lens. Yet the community of clinicians and investigators who appreciate the importance and challenges involved in effective recruitment and retention of older adults in aging research has remained small. All of these issues, together with best practice strategies to overcome obstacles to the recruitment and retention of older adults in aging research, were discussed in the December 2008 issue of this journal.[1] A decade later, it is gratifying to see three articles address the inclusion of older adults in research.[2–4] Timing is perfect given major progress at the national level in the form of a new NIH (National Institutes of Health) policy effective as of January 25 2019 mandating the inclusion of older adults into all NIH-supported research involving human subjects when scientifically appropriate.

Phase III clinical trials represent the last step required for the process of Food and Drug Administration approval so that a clinical intervention may become available as part of routine clinical care. In a report from the National Institute on Aging (NIA) at NIH, NIA program staff examined www.clinicaltrials.gov for the inclusion of older adults in phase III clinical trials targeting the most frequent causes of hospitalization and/or disability including congestive heart failure, cardiac dysrhythmias, coronary atherosclerosis, heart attack, stroke, chronic obstructive pulmonary disease, pneumonia, lung cancer, prostate cancer, and osteoarthritis.[2] Among trials from 1965 to 2015, 33% had arbitrary upper age limits, and 67% reported on subjects younger than those typically afflicted by these conditions.[2] Beyond age, older adults were also excluded on the basis of polypharmacy and comorbid conditions.[2]

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## CHALLENGES REMAIN

These findings add important new evidence to our understanding of the extent, the pervasiveness, and the impact of underrepresentation of older adults in research.[2,5] They also illustrate the manner in which the research community has failed to deal with three cross-cutting issues of key importance to the science and practice of geriatric medicine. First, failure to include individuals with coexisting chronic diseases means that such clinical trials lack relevance or generalizability for typical geriatric patients with multiple coexisting conditions.[3,6] Second, absence of functional outcome measures has resulted from and contributed to a disease-based focus, generating data that fail to respond to patient preferences involving function and independence.[3,7] Third, by emphasizing clinical trials designed to study the impact of interventions on one disease at a time, opportunities for addressing aging as a major shared risk factor for multiple chronic diseases and for the validation of geroscience-guided therapies have been lost.[8]

## ENSURING RECRUITMENT FEASIBILITY AND PROMOTING THE SCIENCE OF RECRUITMENT

The new NIH policy mandating the inclusion of older adults will now force investigators to at least consider age as a variable in recruitment plans and study design. With proper justification, studies addressing problems seen exclusively or mostly in younger populations will not need to include older adults. However, a mere desire to recruit older adults will not suffice. When designing each study, investigators need to select inclusion and exclusion criteria carefully on the basis of the specific questions being addressed.[9] Attention also needs to be paid to the selection of recruitment strategies shown to be most effective in terms of recruitment success, retention, and cost for the specific population being targeted.[1] To that end, there continues to be a lack of research addressing the science of research and recruitment in geriatrics. We know that perception of greater benefit tends to enhance willingness to participate[10] while intrusiveness diminishes it.[11] For many studies, including those involving the administration of influenza vaccines, retention rates may be especially high with repeat participants reflecting more than 80% of enrollees.[12] Mail-based recruitments can be effective[13,14] and less costly[14] alternatives to other approaches such as newspaper ads. Nevertheless, important knowledge gaps remain regarding



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comparative effectiveness and costs, especially when specific subpopulations and settings are involved. The posting by NIA of a funding opportunity announcement for applications related to the science of examining diversity, recruitment, and retention in aging research should greatly accelerate progress.[15] Also, the 5Ts Framework described by Bowling et al in this issue[4] provides practical insights into addressing some of the barriers to participation by non-geriatrician investigators and research staff without experience in aging research and may also help frame future research on this topic.

## PROMOTING THE SCIENCE OF GERIATRIC RESEARCH

Most importantly, the fundamental differences distinguishing aging from other types of research involve much more than the mere inclusion of older adults.[9] Even the question of how one goes about selecting healthy normal older controls depends on whether the goal is to capture the presence of usual or more typical "healthy" aging that may involve the presence of common and well-controlled chronic conditions and use of medications not expected to confound the study question (eg, hypertension, hyperlipidemia, osteoarthritis)[9] or whether one can justify the need, time, and expense of seeking to recruit older individuals without any chronic conditions or medications who reflect exceptional or successful aging.[16]

In terms of populations being targeted through intervention trials, now rendered more relevant for the health of our aging society as a result of the new NIH policy on inclusion of older adults, the American Geriatrics Society report on this topic also published in this issue has raised several additional important points for future consideration.[3] As noted, older adults must not be enrolled in studies in a token way.[3] Their recruitment must be meaningful, scientifically justified, and ultimately mirror the clinical realities experienced by older adults living with these conditions in typical clinical settings.[3] In the past, older adults were often excluded in view of concerns regarding the possibility that coexisting medical conditions and medications among subjects recruited into observational studies and clinical trials could confound associations or treatment outcomes, leading to heterogeneity in treatment responses.[1,17] However, a growing body of knowledge indicates that careful recruitment of older adults with well-defined clinical states in terms of phenotypic frailty or specific clusters of coexisting chronic conditions may offer novel clinical and translational insights into their unique risk factor profiles and pathophysiologic mechanisms.

It is also important to note that in spite of a natural inclination to focus on comparing changes over time in key outcome variables between intervention and placebo groups, this may not be the most efficient approach when the target population includes older adults with multiple, yet variable coexisting chronic conditions. The purpose of randomization is to ensure that the two groups are selected by a process that is truly random, one that is likely to work well when dealing with large numbers.[18] Therefore, comparisons made between treatment and placebo groups at the conclusion of a clinical trial not only represent an efficient and suitable outcome measure, but they may also protect from confounding when dealing with major interindividual variability among trial participants.[18]

With all of the considerations just described in mind, it is quite likely that in another decade we will once again reflect on yet further additional progress and the importance of the issues regarding recruitment of older adults in aging research as highlighted in these three publications.[2–4]

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