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Making General Internal Medicine Research Relevant to the Older Patient with Multiple Chronic Comorbidities

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General Internal Medicine research evolves in response to the needs of the patients to whom we provide care. Currently, many studies exclude older adults who deeply affect the clinical care of this population. With the number of older adults increasing, creating research protocols that include older adults with multiple chronic comorbidities is imperative. Through funding from the Association of Specialty Physicians, a working group of aging-responsive researchers from the Society of General Internal Medicine was convened to tackle this issue. The goal of this article is threefold: 1) to shed light on the current exclusion of older adults in research; 2) to identify and propose research protocol solutions for overcoming barriers to including older adults in research; and 3) to provide suggestions for research funding. The extent to which these recommendations can create change depends greatly on our researcher colleagues. By embracing these challenges, we hope that the care provided to older adults with multiple chronic conditions will no longer be extrapolated, but become evidence-based.

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CURRENT EXCLUSION OF OLDER ADULTS IN RESEARCH

Much of how we practice clinical medicine is based on evidence from quality studies conducted by general internal medicine researchers. In caring for older adults, most clinicians are forced to extrapolate from or adhere to guidelines that are based on studies that have excluded this older adult population. Is it realistic to believe that medical evidence for a 50-Year-old patient would hold support for an 80-year-old patient? When a patient reaches 90 years and outlives their expected lifespan, what research evidence supports their clinical care?

Randomized clinical trials (RCTs) have historically excluded participants over a certain age, resulting in study participants not representing patients seen in clinical practice. A 2004 review of top-tier journals found that only 5 % of published studies focused on older adults.[1] A systematic review of phase III and IV RCTs published in five high-profile journals in 2007 assessed the representation of older adults in these trials. Of the 109 trials included in the analysis, 20.2 % excluded older adults based on age criteria alone: four set an age cutoff for study participation of < 70 years, eight at 70–75 years, seven at 76–80 years and three at > age 80.[2] This represents an improvement from a prior evaluation of published RCTs between 1994 and 2006 that found that 39 % of trials excluded adults over the age of 65.[3] Given the paucity of older adults in clinical trials, clinicians of necessity extrapolate from studies conducted in younger populations to inform their practice. Despite encouragement by federal agencies that researchers report clinical trial data by age and differences in safety or effectiveness associated with age, such guidelines are not sufficient to effect significant change.[4–6]

Older individuals have a higher likelihood of having multiple chronic conditions, complicating study design and analysis. Geriatricians and aging-responsive researchers have been studying multiple chronic conditions for decades. When an intervention is studied in people with multiple chronic conditions, it becomes more difficult to definitively demonstrate an effect. Researchers tend to want to show that what they are studying works. Many trials are sponsored by industry, and the chances of isolating an effect are higher for more pristinely defined populations. One might argue that if an intervention is demonstrated to be effective among older individuals, then it will also be effective for those who are younger or healthier. Practically,

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this does not occur, as this would be setting a higher bar for demonstrating efficacy or effectiveness.

A key issue in research among older adults is complexity. Researchers are trained to conduct "scientifically pure" or single-issue studies. Unfortunately, such "pure" studies, by not taking into account complexity or heterogeneity of treatment effects, may have limited applicability to the geriatrics population, making it difficult to interpret or apply findings. By limiting study populations based on an age threshold, researchers are simplifying the study design, implementation and analysis at the cost of generalizability and applicability of the research findings to real-world populations. Study designs have not sufficiently evolved to address the needs of a growing older population. The continued use of arbitrary age thresholds for study eligibility may reflect inattention or complacency on the part of researchers. Since 65 years of age has been defined as "geriatrics" for many years, researchers may utilize 65 years of age, or other age thresholds, without thoughtfully considering the implications of the age threshold for the study question. Researchers need to change their cognitive framing regarding the role of age as a study exclusion criterion.

The population imperative, the demonstrated lack of inclusion of older adults in clinical trials, and the consequent lack of evidence that is directly applicable to care of and policy decisions regarding older adults should make this high priority for our specialty. In addition, focusing on, or at least thoughtfully including, older adults in research opens a whole new range of research funding mechanisms. It may not require changing a research focus, but rather leveraging the studies that are already being conducted; for example, by following cohorts over time as they age, adding geriatrics-relevant outcome measures, or explicitly expanding study populations to older adults. Generalist researchers should embrace the complexity of studying this population, as well as conducting research that truly advances understanding of the phenomenon and is applicable to the populations of interest. Just because it is difficult, doesn't mean it shouldn't be done.

BARRIERS AND SOLUTIONS TO INCLUSION OF OLDER ADULTS IN RESEARCH

This working group proposes a number of approaches to facilitate research with older adults with multiple chronic conditions, minimizing as many of the identified barriers as possible. By doing so, we hope to demonstrate that incorporating older adults in studies is achievable and that these principles apply in the varied settings (e.g. hospitals, primary care or consult practices, nursing homes, or homes in the community) in which such studies may be conducted.

Elimination of Age Cutoffs

There is a long-standing adage that "age is just a number". Given the heterogeneity in clinically important characteristics among individuals of the same chronologic age, age may no longer need to routinely be considered as criteria for study enrollment. While there may be cases in which age is an appropriate eligibility criterion, such as when studying changes in utilization based on eligibility for Medicare at age 65 years, for many studies, clinically important criteria should be utilized instead. Eligibility criteria could be defined and based on characteristics that travel with age, not age itself (e.g. functional status, cognitive capacity).

Cognitive Impairment and Capacity to Consent in Older Subjects

The prevalence of cognitive impairment increases with age, which makes obtaining informed consent from seniors complicated at times.[7] Research has shown that older adults with very mild to moderate Alzheimer's disease (MMSE $\geq$ 23) may well retain sufficient capacity to consent.[8] Well-meaning institutional review boards (IRBs) often compel exclusion of individuals with cognitive impairment in the interest of protecting them; instead, such blanket exclusion may actually be harmful, preventing generation of evidence that may benefit this population. Acceptable approaches to including individuals with cognitive impairment in studies vary between IRBs and grant reviewers, often frustrating researchers. Consequently, there is a need for more explicit rules or a common language governing the inclusion of cognitively impaired people in research. Our group has developed the following framework to assist researchers in including older adults with cognitive impairment in research:

1. First, are the older adults with cognitive impairment currently making their own medical care decisions? It is not a breach of confidentiality to ask a treating physician if a patient is eligible for a study or is able to participate in the informed consent process for study participation. If the individual is not able to make his or her own medical decisions, or is deemed unable to comprehend the complexities of consent for study participation, researchers must involve a proxy informant ("legally authorized representative") in the consent process.[9]
2. Involving a proxy informant or a power of attorney (POA) is necessary for recruiting and enrolling potential study participants who are not able to make their own medical decisions, and thus are not likely to be able to provide informed consent for study participation. For potential study participants without an established POA, prior research studies have used a

proxy decision maker to make decisions about study enrollment.

3. The decision about the need for a proxy to provide informed consent should be separate from the decision regarding the need to for a proxy informant to obtain study data. A proxy informant may not need to be present at all aspects of the data collection, dependent upon the study interventions and outcomes.
4. Regardless of patient ability to consent, we recommend involvement, through data collection and education, of surrogates and/or informal caregivers when possible in studies involving cognitively impaired older adults. In all studies, caregiver burden—of the caregiving and of study participation—should be considered in the study design and compensated appropriately (e.g. offspring who miss work to bring senior parents to a study visit).
5. Where caregiver or proxy informant responses are being solicited, it is imperative to understand the actual roles of the respondent. For example, while some caregivers may have significant responsibilities related to medication management or other components of the day-to-day care of the study participant, others may solely be responsible for transportation, and so be less knowledgeable about key study variables or outcomes.
6. Occasionally, a high-functioning study participant is consented, and mid-study is found to have diminished cognition and questionable decisional capacity. While some may argue that these individuals should be withdrawn from the study when they are found to have diminished cognitive capacity, doing so has the potential to introduce significant response bias. Planning for the development of cognitive impairment in the study design, for example, inclusion of a proxy respondent from the beginning of the study, could circumvent the potential lost data. For example, the Health and Retirement Study (HRS) has accommodated participants becoming cognitively impaired over time through intensive planning. The HRS permits a proxy interview to be conducted when an individual is unable to do so because of cognitive limitations.[10] Our group recommends emulating the HRS standard protocols on troubleshooting these cognitive issues. By continuing to include data from these participants, studies will have better validity and generalizability for older adults.

These recommendations are relevant to investigators, IRB members, journal editors, and grant reviewers—anyone involved with design, conduct, review or oversight of studies relevant to older adults. Looking forward, not all studies can accommodate individuals with cognitive impairment. In these cases, investigators should explicitly address the issue and give a valid reason why cognitive impairment is a legitimate exclusion criterion.

Burden of Survey/Measurements

Researchers who study older adults frequently encounter the question of study burden for seniors. How long a survey is too long for older adults? Older adults are not identical and should be treated individually. A balance between the study integrity and the needs of study participants is crucial. Where able, researchers may need to avoid "one size fits all" approaches, and instead use flexible study designs that tailor to the individual (e.g. either a 2-hour survey or two hour-long surveys). While IRBs attempt to ensure people are not overburdened, a longer survey performed once may be safer and less burdensome than requesting the participant to return to complete the second half. Older adults may find it difficult to arrange transportation for data collection, and coming once or data collection through a home visit may be more acceptable. The best means of reducing subject burden is through thoughtful planning and thorough education and training of research staff. At planned intervals, research staff should re-assess how the participant is feeling and reinforce that break times are encouraged. Dependent on the study locale (e.g. hospital or nursing home room without frequent visitors), older adults may potentially enjoy a participation in a longer survey if it provides socialization and sharing of past experiences.

Inclusion of Individuals Residing in Skilled Nursing Facilities or Long-Term Care Settings

Researchers conducting studies among the older adult population will encounter individuals who reside in skilled nursing facilities or long-term care (LTC) settings (e.g. nursing homes, assisted living). Questions arise as to (1) whether IRB approval is required at each facility, (2) whether study participants who have been recruited/consented elsewhere and transfer to a facility requires re-consent or facility notification, and (3) how to handle facility administrative changes that affect study collaborations or conduct of research. Where able, we recommend inclusion of the medical director or other clinical leadership at each site where study participants may be enrolled or admitted during the course of study participation. Ideally, approval from a single IRB may sufficiently cover all transitional care settings similar to what is being discussed nationally for multi-center trials.[11] When previously enrolled in IRB-approved studies and transferred to LTC settings, the study participants should be the true determinants of whether they wish to continue study participation. It is an infringement of resident rights for care facilities to obstruct a resident's wish to participate in research when it does not affect other residents, staff, or patient safety.

MEASURABLE OUTCOMES PERTINENT TO OLDER ADULTS

Mortality and morbidity are commonly used research outcomes. Considering their multiple chronic comorbidities and natural proximity to mortality, older adults may not benefit from research utilizing these outcomes. We propose that focusing on quality of life, particularly related to functional status, would have a greater influence on clinical decision making among the older adult population.[12,13] Tinetti et al. has proposed the idea of universal health outcomes, such as symptom burden, functional capacity, and self-rated health, since they have been deemed important by older adults.[14] These universal outcomes can be used to study the effects of multiple conditions and their treatments. Family/caregiver outcomes should also be considered, including burden, emotional and physical health, quality of life as well as economic factors (e.g. caregivers' missed days from work, time to transport patient, time providing direct care to patient).

Researchers may be concerned that including older adults with comorbidities in studies may inadvertently increase adverse events, entailing burdensome reporting. Researchers should address this issue proactively in the study design, determining a means of assigning "relatedness" to the underlying condition versus the intervention under investigation. Events relevant to geriatrics, such as falls, incontinence, or delirium, should be routinely measured in this population; however, whether or not these are treatment-related adverse events should be decided within the context of the study. It is important to note that many important outcomes are also potential adverse events that are not captured by traditional disease-oriented adverse event monitoring. An intervention may have adverse effects on function or other universal outcomes, and thus adverse event monitoring should include the same geriatric-oriented indicators as are used as outcomes.

Common Measurement Tools Available in Geriatrics Research

A misconception exists that incorporating measures relevant to geriatrics will adversely lengthen most studies, increasing costs. A number of validated measurements for high impact geriatric conditions exist that can be easily incorporated into study protocols. Table 1 proposes a brief battery of geriatrics outcomes and recommendations from our group on potential measures. While this table of geriatric conditions and assessments is not all-encompassing, it provides a starting point for researchers interested in incorporating older adults in their studies.

There remains a number of needs or gaps in geriatrics-relevant measures. The Lachs assessment instrument is a short comprehensive evaluation of geriatric conditions; more work is needed to divide it into usable components.[26] Additional measures are needed for study of individuals that older adults depend on but are understudied, such as paid or formal caregivers.[27]

Table 1. Practical Tools to Measure Geriatric-Relevant Outcomes

Geriatric-relevant outcomes	Proposed brief assessments
Cognition	Mini-Cog[15] Short Portable Mental Status Questionnaire (SPMSQ)[16] Montreal Cognitive Assessment (MOCA)[17]
Physical function	Activities of daily living[18] Instrumental activities of daily living[19] Karnofsky performance scale[20] Australia-modified Karnofsky performance scale
Symptom burden	Condensed Memorial Symptom Assessment Scale (CMSAS).[21]
Mobility/ falls	Timed up and go test[22]
Delirium	Confusion assessment method[23]
Depression	PHQ–9[24] Geriatrics depression scale[25]

Further Incentivizing Research with Older Adults

Research that includes older adults needs to be incentivized. Although older adults account for a significant portion of health care utilization and expenditures, older adults are under-represented in research, even for conditions that have a higher prevalence in the older population. Many research results are thus extrapolated to seniors from younger cohorts. Older adults should thus be treated as an under-represented population. Funders, editors, and reviewers should set the standard that older adults are included in all research studies, unless exclusion is well-justified.

The National Institutes of Health (NIH), as a major funder of research, has long championed inclusion of under-represented populations in studies. Most notably, targeted enrollment tables and inclusion sections (e.g. women, race, ethnicity) are required elements of grant applications to ensure that all populations are studied. To ensure older adults are included in NIH-funded research, a targeted enrollment table specific to including older adults could become a requirement (Table 2). In some studies, there will be an appropriate reason to exclude older adults, but this would need to be justified in a section for inclusion of the

Table 2. Proposed NIH Grant Application Enrollment Table for Inclusion of Older Adults

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Age Categories (years)	Females	Males	Total
0-21			
22-39			
40-64			
65-79			
>80			
Age Categories: Total of All Subjects			

aged, as is required for children, women and diverse racial/ethnic representation.

CONCLUSION

These recommendations will only be as useful as the extent to which they are effectively disseminated to, and implemented by, researchers working towards advancing care for older adults. Through these recommendations, this working group hopes to positively impact the inclusion of older adults in research studies. Currently, older adults are not regularly included in research, which directly affects how physicians approach care for their older adult patients. Only by including older adults in research will we be able to provide evidence-based care to a growing population. It is our hope that general internal medicine researchers will continue to be on the forefront of conducting rigorous and thoughtful research that impact our population, including older adults. If we are fortunate enough to continue aging, we may all benefit from research studies that include older adults.

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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