Excluding Older, Sicker Patients from Clinical Trials: Issues, Concerns, and Solutions

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This Insight on the Issues discusses issues, concerns, and possible approaches to expanding clinical trials to include older people and those with chronic conditions to make research more relevant for clinicians treating these people.

Background

People with multiple chronic conditions (also referred to as comorbidities) represent more than one-quarter of all Americans and are responsible for 65 percent of all health care utilization. As people get older, the prevalence of chronic conditions increases. Medically complex, older patients account for a disproportionate share of health care services, use more prescription drugs and medical devices, and experience more complications and adverse drug events than younger, healthier patients. By the time they reach Medicare eligibility, one-quarter of the population has five or more chronic conditions and is responsible for more than two-thirds of Medicare spending.

Clinical trials are intended to test the efficacy and safety of medical interventions, such as prescription drugs, medical devices, and surgical procedures. Medical researchers perform clinical trials to obtain reliable, unbiased information about the effects of various clinical interventions on patients with a target illness or condition. By comparing the effects of a discrete intervention on one group of patients, the treatment group, with the effect of standard or routine therapy on a second group of patients, the control group, researchers seek to isolate the treatment effect from other factors, such as age, sex, and health status. In the most rigorous form of clinical trials—randomized controlled trials (RCTs)—members of a single group of volunteers are randomly assigned to either a treatment or control group. Differences in the clinical outcomes experienced by otherwise similar patients are assumed to arise solely from differences in treatment.

The Problem

Most hospital and physician encounters involve older people with multiple chronic conditions. Yet clinical trials often exclude or under represent this group of people. This underrepresentation is not limited to prescription drug studies but encompasses the full range of medical interventions, including medical devices and procedures. Underrepresentation of older, sicker adults in clinical trials makes it difficult to understand the full impact of medical interventions and may lead to inappropriate use of interventions in these populations. A report from the U.S. Food and Drug Administration (FDA) finds that adults over 50 are more likely to experience a more intense and greater variety of side effects to any single medication than other adults.¹
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Clinical Trials Often Exclude Older, Sicker Patients

Many clinical trials explicitly exclude older, sicker patients. Even in trials without explicit exclusion criteria, the percentage of older adults included is low. A comprehensive study of the extent to which RCTs published in major medical journals have excluded certain patient populations found that, over 12 years (1994–2006), 81 percent of trials excluded complex, older patients with common medical conditions, while 72 percent excluded patients on the basis of age.2

While the prevalence of age-based exclusions per se is declining, exclusions based on comorbid conditions are increasing, which also has the effect of excluding older adults. A study of RCTs published in five major medical journals in 2007 found that 46 percent of studies excluded patients based on criteria such as physical or functional limitations, cognitive impairment, or shortened life expectancy, and 20 percent excluded patients based on an upper age limit. These criteria disproportionately exclude older adults.3

RCTs conducted internationally also exclude or under represent older adults and people with co-morbidities. A study of trials under way in the United States and Europe in 2008 of patients with heart failure found that 80 percent excluded patients with comorbidities and 25 percent excluded patients on the basis of an arbitrary upper age limit.4

While many studies have successfully recruited medically complex, older patients, the majority of trials are not recruiting them proactively. Physicians raise a number of concerns about recommending that their patients participate in clinical trials, such as doubts about their patients’ ability to adhere to complex trial regimens and about the risks and benefits of participation. Anecdotal evidence suggests that many researchers incorrectly assume that older and sicker adults do not want to participate. However, this exclusion is often poorly justified. Many older people want to participate in clinical research for a range of reasons, from altruism to self-interest. Further, there is little evidence to suggest that older patients cannot tolerate or benefit from participation in clinical trials. In any case, methods for increasing the participation of older patients are available.5

Arbitrary exclusions, particularly of a patient population at higher risk of the clinical condition, raise questions regarding the generalizability of clinical trial results and their relevance for routine clinical practice. For instance, a study of 20,388 Medicare beneficiaries with heart failure who were discharged from acute care hospitals in the United States found that only 13 to 25 percent met the enrollment criteria of three landmark RCTs that have influenced the treatment of all patients with congestive heart failure.6

Research based on clinical trials that have excluded complex, frail, older patients can produce findings that are incomplete or of dubious relevance, leading to poorly founded practice guidelines and quality of care measures. In this case, clinicians may be faced with a “risk-treatment paradox” in which high-risk patients are denied safe interventions capable of materially improving survival and/or quality of life or, on the other hand, receiving inappropriate interventions in which risks are likely to outweigh benefits.

Physicians may also face a dilemma when seeking to apply multiple practice guidelines that conflict or are incompatible because the evidence on which they were based did not take
adequate account of patients with multiple chronic conditions.

Although the FDA has published guidelines for the study of drugs likely to be used in the older population, these guidelines do not include specific standards governing the inclusion of older people or those with complex medical conditions in clinical trials for drugs or devices.\(^7\)

Another obstacle to expanding clinical trials is the cost of the intervention. While Medicare will pay the cost of routine patient care for beneficiaries enrolled in FDA-approved clinical trials, Medicare and most private insurers will not cover the cost of items or services that are considered experimental or investigational. In many cases, these costs are borne by the trial sponsor. In some cases, patients may be required to bear these costs.

There is general agreement in the scientific and clinical communities that underrepresentation of older adults and people with multiple chronic conditions is problematic. However, there is less agreement about the best approaches to address this problem.

Proposals to expand participation in clinical trials have raised a number of issues related to the following:

- Safety and ethical considerations
- Efficacy and effectiveness
- Costs

**Safety and Ethical Considerations**

Safety concerns around expanding clinical trials include potentially higher rates of morbidity and mortality among populations that may be frail and at heightened risk of complications, and thus more prone to suffer serious adverse outcomes and side effects in trials.

Yet the exclusion of older people or those with multiple chronic conditions also raises safety concerns. FDA rules allow off-label use of prescription drugs for patients with characteristics that were not represented in clinical trials in which the drugs were tested. Off-label use of many prescription drugs is often higher in older populations (e.g., antipsychotics for agitation in older people). Because older, sicker patients are often underrepresented in trials, understanding of their response to off-label use of a drug (such as side effects, adverse reactions, and interactions) may be incomplete. The ongoing practice of off-label use suggests the need to include populations with these characteristics in clinical trials.

Some experts feel it is unethical NOT to include these populations in trials, since they represent a large percentage of the people who receive drugs and other medical interventions. These experts contend that it is better to include these people so as to identify issues in a controlled setting where adverse effects can be monitored and addressed, rather than leaving practitioners and patients to fend for themselves in unsupervised environments. However, participating in clinical trials may place older, sicker patients at unnecessary or disproportionately higher risk without the likelihood of commensurate benefit, raising ethical concerns.

These competing concerns raise questions about whether clinical trial participation must be in the best interest of the patient or can be conducted for the benefit of future patients and practitioners, even though the patient might be placed at increased risk. Concerns about the safety and ethics of expanding trials raise questions about whether safety concerns can be separated from ethical concerns. Such questions suggest that issues related to expanded trial participation may deserve
further analysis from an ethical perspective.

**Efficacy/Effectiveness Considerations**

When trying to design trials that produce more relevant and generalizable results for clinicians caring for older, sicker patients, the goal is to include trial participants who are similar to patients whom clinicians typically face in routine practice. Such trials, known as pragmatic clinical trials, are likely to include patients who are older and more medically complex (i.e., more heterogeneous) than most current trial participants. However, there are legitimate scientific concerns about making trials more heterogeneous. For instance, due to the variety of factors that may affect outcomes, such trials are likely to make reliable measurement of the intervention effect more difficult.

Whether more relevant and reliable results can be obtained by expanding trial participants to include older, sicker patients (or by conducting separate trials dedicated to such populations) is likely to depend on the specific intervention and the characteristics of the populations for whom relevant results are desired—for example, whether the target population is middle aged and relatively healthy (homogeneous) except for the target illness, or older and sicker (heterogeneous).

In addition, in order to ensure a comparable level of confidence in the results of a heterogeneous trial and draw conclusions about specific subpopulations, the number of trial participants must be increased, sometimes substantially, compared to a more homogeneous population. In any case, when enrolling more heterogeneous populations, it may be difficult to predict the level of potential differences in treatment effects and, thus, to estimate the trial size necessary to obtain reliable results.

When selecting outcome measures for trials, in addition to measuring the impact of an intervention on morbidity and mortality, it is important to include patient-centered measures that reflect the values of the target population. At the same time, the response burden of additional measures on trial participants and sponsors’ resources must be considered. In order to give advice based on individual patient priorities, clinicians need relevant information on patient-centered measures. For instance, older, sicker patients may value an intervention’s effect on quality of life (i.e., function and comfort) as much as or more than its effect on morbidity and mortality. Collecting data on standardized quality-of-life measures across all trials could increase the relevance and comparability of trial results, but it could also add significant cost to trials.

**Cost and Business Considerations**

Increasing the proportion of older, sicker patients could increase costs associated with conducting clinical trials. A larger number of patients could be required to ensure the numerical power necessary to achieve statistical significance among subgroups in a more diverse population. Increasing sample size, particularly with older, sicker patients, could produce more adverse events, which could increase monitoring costs. The cost of follow-up efforts could also increase due to changes in seasonal residence and more deaths during the trial.

On the other hand, expanding the pool of potential participants could make recruiting patients and trial sites easier and faster. Accelerating the recruitment process could shorten the duration of trials and lower the screening-to-enrollment ratio of participants. These
measures could reduce the number of trial sites and administrative personnel. Relying on centralized follow-up and monitoring facilities might also reduce costs. Shortening the duration of clinical trials could accelerate the time to get commercial products to market and generate revenue that would offset the cost of research and development.

Whether the net effect of these changes would increase or decrease costs would depend on the trial. Performing case studies and computer simulation models for several types of trial cases and their costs could improve our understanding of the interaction of various factors that might affect total cost.

As a competitive matter, industry funders may be concerned that expanding inclusion criteria could increase the cost of trials and produce a less favorable profile of results, particularly adverse effects, when compared to competing interventions that were previously tested under narrower inclusion criteria.

Rather than expanding clinical trials to include older, sick patients, resorting to dedicated clinical trials that include mostly older, sicker patients could produce more relevant and reliable clinical data. This approach could avoid the added complexity associated with conducting more trials that enroll more a homogeneous, low-risk population. However, undertaking dedicated trials specifically focused on medically complex, older patients would add the cost of these trials to the total cost of obtaining information about these populations without offsetting savings. Some experts feel it is unrealistic to expect separate trials to be undertaken specifically for older adults and/or multiple chronic conditions. Unfortunately, funding remains inadequate to sufficiently expand geriatric research. 

The following are lower cost alternatives to clinical trials dedicated to older, sicker patients:

- Informal trials in which patients serve as their own controls during randomly sequenced periods of use vs. nonuse
- Post market surveillance during which data are collected and analyzed following FDA approval to market a drug or device
- Observational data analysis using data collected for non-research purposes, such as insurance claims data
- Relying on expert opinion through consensus guidelines, rather than performing trials

However, each of the alternatives has limitations, including less validity and reliability than RCTs.

Discussion

A number of policy options are available to address inappropriate exclusions and expand clinical trials to include older people and those with multiple chronic conditions. However, many of these options could be controversial and potentially costly. Some options would require further development and testing before implementation. The following list is offered merely to identify possible policy options and is not intended to represent an endorsement or even a ranking of their relative strengths and weaknesses.

- Federal agencies could take the initiative to ask whether older adults or people with multiple chronic conditions will be included in proposed trials.
  - The Department of Health and Human Services has established a “Strategic Framework for Multiple Chronic Conditions”
that calls for ensuring that individuals with multiple chronic conditions are not unnecessarily excluded from clinical trials.9

— Broader inclusion criteria could be made part of federal research grant-scoring criteria, much as the National Institutes of Health (NIH) established policies in the mid-1980s for inclusion of women and minorities in clinical research.10

■ Post market surveillance studies could be undertaken to assess adverse drug reactions arising from prescribing patterns for older adults and people with multiple chronic conditions compared to younger, healthier populations.

■ Institutional review boards, which must give prior approval for clinical trials, could encourage investigators to adopt broader inclusion criteria for proposed trials.

■ Medical journals could encourage broader inclusion criteria through their publication guidelines and manuscript selection process.

■ Public payors, such as Medicare and the Department of Veterans Affairs, and private payors, such as health insurers and employer health plans, could offer “conditional coverage” for experimental and investigational items and services that are not currently covered, as long as they are furnished as part of an approved clinical trial, to encourage research on older, sicker patients.

■ The FDA could require label warnings regarding use of drugs and devices for older, sicker patients.

— Such warnings might be designed to reduce the risk of avoidable complications in vulnerable populations for which the products have not been tested.

— However, the FDA could not extend such protections to use of procedures that it does not regulate.

■ Congress could create financial incentives to encourage manufacturers to expand clinical trials to include older, sicker patients by offering longer exclusivity for drugs, devices, and procedures that have been tested on such patients through extended patent protection, exclusive FDA approval, and favorable Medicare reimbursement policies.

— For example, “orphan drugs” currently receive extended exclusivity through the FDA approval process.

■ Congress could mandate expanded participation in federally funded clinical trials.

— For example, Congress has previously mandated inclusion of women and minorities in clinical trials when it codified similar NIH policies in 1993.11

— Until effective approaches and potential pitfall have been adequately explored, mandating expanded clinical trials could have unintended consequences
Endnotes


