THE AMERICAN GERIATRICS SOCIETY

UNDERREPRESENTATION OF OLDER ADULTS IN CLINICAL TRIALS

ISSUE BRIEF

What are Clinical Trials?
Clinical drug trials are research studies designed to evaluate the safety and effectiveness of drug therapies. They are key to understanding the appropriate use of medications, and informing payers about which ones to cover.

Are older adults well-represented in clinical trials?
Unfortunately, despite recent improvements, older adults are significantly underrepresented in clinical drug trials. This disproportionately low participation is troubling and potentially dangerous, given that the reactions of older adults to medications may differ significantly from the reactions of younger participants. After years of being excluded from virtually all clinical trials, recent federal reforms mean that older Americans are, in increasing numbers, finally finding their way into such trials -- but more remains to be done to educate older adults, health professionals, policymakers, and the public about the importance of including older patients in clinical research to ensure drug safety and effectiveness across a broad spectrum of older Americans.

Why is this issue important?
The elderly comprise the fastest growing subpopulation and constitute an increasing proportion of the total population compared to other age groups. By the year 2030, the number of persons in the United States 65 years of age and older will double and the number of those over 85 will quadruple.[1] The elderly use a disproportionately larger amount of health care resources since they experience a higher incidence of disease-related morbidities, consume more drugs, are subject to more extensive multiple medication regimens, and account for more adverse drug events than their younger counterparts. Drugs improve the quality and length of life for this growing population of older Americans who often take multiple medications on a regular basis.

According to a 2006 report, 83% of men and 80% of women used at least one prescription drug in a given week. In the oldest age group, more than one in four patients were using five or more prescription drugs in a given week.[2] Before the implementation of Medicare Part D, the average Medicare beneficiary filled anywhere from 21-36 prescriptions annually.[3] Projections by the Congressional Budget Office estimate that over the next ten years, federal taxpayers will subsidize $558 billion in drug purchases for Medicare beneficiaries under the Part D drug program. In response to the great demand for geriatric pharmacotherapy, the pharmaceutical industry has targeted more drugs to the elderly.[4] In 2005, more than 900 drugs being evaluated in clinical trials were aimed at treating diseases or conditions associated with aging, according to the Pharmaceutical Research and Manufacturers of America.

Since older adults generally take the most medications, they are most likely to be among the first to use newly available drugs. Further, adults over age 50 are more likely to experience a more intense and greater variety of side effects to any single medication than other adults.[5] This is largely due to the fact that as people age, they generally experience a decline in kidney and liver function. This change affects the way drugs are processed, causing them to stay in the body longer and leading to an increase in side effects such as dizziness, drowsiness, falls, depression and insomnia. The increase in the intensity and variety of drug side effects in the elderly is also due to the fact that older adults take more medications than their younger counterparts, and the reaction to medications multiplies disproportionately as the number of medications taken increases. Therefore, inclusion of older adults in clinical trials makes the identification of potential side effects more likely.

In an ideal world, data from clinical drug trials would describe how a given drug is likely to affect older patients differently from younger ones.[6] Although pharmaceutical companies are required to include a geriatric use section with their products, the information is often inadequate and practitioners are often forced to extrapolate from clinical trials conducted on young adult subjects.[7] This lack of information on the elderly population can contribute to increased drug-induced morbidity and mortality.

Are there guidelines to ensure the adequate representation of older adults in clinical trials?
Despite the fact that medical researchers have long pointed to age-related differences in how drugs are absorbed, metabolized and excreted, it wasn't until 1989 that the Food and Drug Administration (FDA) published *Guidelines for the Study of Drugs Likely to be Used in the Elderly*, which stated that the population studied should reflect the population likely to be treated.[8] While recognizing that participation of the elderly may not be possible in some cases due to patient safety issues or the potential for confusion in study results, the *Guidelines* conclude that "[a]ttempts should … be made to include patients over 75 years of age and those with concomitant illness and treatment, if they are stable and willing to participate."[9] Unfortunately, no specific regulatory standards govern inclusion of older persons in clinical trials, and a number of recent studies confirm that rather than being oversampled in clinical trials, to reflect their distribution in the drug consuming population, elderly people are inadequately represented.[10]

Have there been studies of inclusion of older adults in clinical trials?
One study published in 1999 in *The New England Journal of Medicine* looked at more than 16,000 cancer patients in clinical trials and found that only 25 percent of the enrollees in the trial were 65 years of age and older, despite the fact that those 65 years of age and older account for more than 60 percent of all cancer cases.[11] Cancer patients who were 70 years of age and older accounted for only 13 percent of clinical trial enrollees, although this population accounts for 47 percent of all cancer cases in the US. Most striking was enrollment for breast cancer patients age 65 years and older. Participants in this group made up a mere 9 percent of enrollees, yet they make up almost half of all cancer cases.

Another study published in 2001 in the *Journal of the American Medical Association* found that the elderly are underrepresented in the clinical trials of acute coronary syndromes (ACS).[6] Despite the

fact that up to 60% of Myocardial Infarction (MI) deaths occur in patients 75 years of age and older and that elderly patients experience more MI complication including heart failure, shock, and ventricular rupture, the elderly are still under-enrolled in clinical trials compared to younger individuals. This study found that between 1966 and 1990, only 19% of ACS trials enrolled any patients 75 years of age and older. During this time period, the elderly accounted for a mere 2% of all patients enrolled in these trials. Since 1990, enrollment increased to 9% and for those studies published since 1995 enrollment increased to 10%. Despite minor improvements, more than half of ACS trials published from 1996 through 2000 failed to enroll at least one patient 75 or older.

In a study published in 2003 in *The Journal of Clinical Oncology*, researchers looked at over 59,000 patients between 1997 and 2000 and found only 32 percent of the participants were 65 years of age and older, although this population represents 61 percent of new cancer cases.[12] Another study published in 2005 in the *Journal of Gerontology* found that those aged 80 years or older (described as Very Elderly Subjects or VES) constitute a special population as they frequently present multiple diseases and therefore results from trials on general adult populations cannot be extrapolated to very elderly subjects.[13] Unfortunately, those 80 years of age and older are often commonly excluded from randomized clinical trials solely based on their age alone. Researchers looked at 84 randomized controlled trials on very elderly subjects published between 1990 and 2002, comparing them with matched trials on general adult populations. The trials covered most of the disease areas of geriatrics. The study found that few trials include very elderly subjects and sometimes neglect certain diseases. Researchers concluded that the inclusion of very elderly subjects in trials on adults should be strongly encouraged.

Why Are Older Adults Underrepresented in Drug Trials?

Older adults may be underrepresented in clinical trials for a number of reasons.[10] To start, patients, family members and/or physicians often have negative notions concerning the benefits of older patients enrolling in clinical drug trials[12] and some trials exclude participants based on age alone. For example, in a survey of American oncologists, although 80% of the respondents agreed with existing data that patients have better outcomes when part of a clinical trial, 50% indicated that they declare patients unfit for clinical trials based on age alone. However, there is little data that suggests that older adults cannot tolerate or benefit from clinical trials.

Older adults are also unrepresented because the trials often have exclusion criteria that are most likely to affect older adults, such as exclusions for people who have multiple diseases and take multiple medications.[11] The 2003 *Journal of Clinical Oncology* study cited above provides a good example. The majority of cancer trials examined in that study prohibited participation if a person had hematologic, hepatic, renal, or cardiac abnormalities, and about 80% of the trials required that enrollees be ambulatory and capable of work or capable of caring for themselves. Other trials looked at for that study excluded patients with certain psychiatric diseases, such as Alzheimer's disease, which mostly affects the 65 and older population.

Two other common barriers to participation are cost and transportation. Many older adults may have a difficult time getting to and from the study site and are therefore unable to participate.[5] Barriers to participation due to cost were eased to some degree in 2000, when Medicare began

allowing payment of routine patient care costs for beneficiaries enrolled in clinical trials.[14] Examples of these routine costs include room and board for a hospital stay that Medicare would pay for anyway, an operation to implant an item that is being tested, and treatment of side effects and complications of the new care. Beneficiaries are, however, required to pay for the new item or services that the study is testing (unless Medicare pays for it otherwise) as well as any coinsurance and deductibles.

How can we address underrepresentation of older adults in clinical trials?
By not including older adults in drug trials, the full potential impact of new drugs on this population simply cannot be fully understood and may have serious and unexpected repercussions for the health of this population when they are provided the medication. This is troubling in terms of the impact on the health of older adults. In addition, many of the drugs tested in these clinical trials are ultimately prescribed to older adults under Medicare Part D, which is subsidized by taxpayers.

Possible ways to address the lack of representation of older persons in clinical trials include:

- Identifying older persons as a special population and implementing policies calling for their inclusion in government-supported research as has been done with women and minority populations.

- Creating incentives, such as a patent extension, for inclusion of older adults in industry-supported research. This has already been implemented for drugs studied in pediatrics.

- Enacting laws and policies to ensure that all drugs prescribed to older adults are tested for their use in this population.

- Persuading health care workers to highlight the importance of clinical trials to their patients, and encouraging them to enroll in studies.

- Allowing Medicare coverage of healthcare costs during clinical trials.

- Closely examining each protocol exclusion criteria in clinical trial design to be sure that it is scientifically justified for the particular trial.

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