

Elders Predominantly Excluded From Research & Clinical Trials

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Whether treating cancer or incontinence, physicians must rely on clinical trials to guide them in diagnosis, treatment and prescription. Consequently, limited representation by a major component of trial populations can lead to a group's exclusion from beneficial forms of treatment or, at worst, late diagnoses and avoidable morbidity and mortality.

Researchers who have studied thousands of published papers and editorials say this problem is uncannily common among the elderly. They contend older people are being excluded from clinical research.

One group of investigators, led by Arup K. Banerjee, MD, a consultant with the Department of Medicine for the Elderly at Royal Bolton Hospital, in Bolton, England, found that one-third of the 1,012 original research papers in major medical journals excluded elderly people without justification (*BMJ* 1997;315:1059).

In a 2005 editorial in the *British Medical Journal* (2005;331:1036-1037), Marion E.T. McMurdo, MD, head of Ageing and Health at Ninewells Hospital and Medical School, in Dundee, Scotland, and colleagues wrote that after repeating the study by Royal Bolton, not much improvement was found.

"We ... found that although matters have improved a little, almost 15% of papers still unjustifiably excluded older people, and that fewer than 5% of the papers published were specific to older people," the authors wrote.

It seems the exclusion of older people exists regardless of the seriousness of the illness. Despite the fact that more than 20,000 women over the age of 70 undergo surgery for stress incontinence each year, a review of trials found that only 3.8% of that age group was represented.

"Older patients are significantly underrepresented in cancer clinical trials," wrote Carol A. Townsley, MD, a clinical fellow working in the Robert & Maggie Bras and Family New Drug Development Program at Princess Margaret Hospital, Toronto, Canada (*J Clin Oncol* 2005;23:3112-3124). Dr. Townsley and colleagues undertook a literature review "to identify barriers that impede the accrual of this vulnerable population onto clinical trials and to determine what specific strategies are needed to improve the representation of older patients in research studies." After reviewing nine of 31 relevant papers from 159 citations, they concluded that "age is a significant barrier to recruitment; only a quarter to one-third of potentially eligible older patients are enrolled into trials."

An argument can be made that this bias has extended from clinical trials to treatment of the elderly. Writing in the *Journal of the American Medical Association* (2005;294:2703-2711), John Milburn Jessup, MD, professor of oncology and surgery, New England Deaconess Hospital, Boston, and colleagues concluded, "Adjuvant chemotherapy use has increased from 1990 to 2002 for patients with stage III colon cancer with an associated increase in five-year survival of 16%. The benefit of adjuvant chemotherapy seems to be lower in black patients and high-grade cancers. Women have the same benefit, but are less often treated. Elderly patients have the same benefit as younger patients, but are less frequently treated."

Older patients have their limitations, which can present hurdles for researchers. The Royal Bolton researchers noted that reasons

for exclusion may be due to the time-consuming job of obtaining approvals from family members and caregivers. Researchers may also fear that subjects are too frail and may be at increased risk from the study. "But we believe that such risks are best investigated in the rigorous setting of a clinical trial," the researchers wrote. "Selected elderly patients can enter trials without being put at an increased risk of more severe or frequent side effects."

In her study published in *Clinical Cancer Research* (2006;12:2141-2149), Dr. Townley noted that "age alone should not be a barrier in the administration of targeted agents." Researchers from the Princess Margaret Hospital Phase II Consortium in Ontario began from the premise that the tolerability of molecularly targeted agents in older patients had not been specifically examined. The team analyzed 401 patients from 19 different studies, who received 1,252 treatment cycles. They concluded that "older patients seem to tolerate molecularly targeted therapies either alone or in combination with chemotherapy as well as younger patients. Age alone should not be a barrier in the administration of targeted agents."

The implications of these findings for pharmacology are also noteworthy. Researchers from the Duke University School of Medicine, Durham, N.C., writing in the *Archives of Internal Medicine* (2004;164:1621-1625), found that 21% of patients age 65 and older ordered from a national benefits manager's database of drugs to be avoided in elderly populations. "Amitriptyline and doxepin accounted for 23% of all claims ... and 51% of those claims were for drugs with the potential for severe adverse effects," wrote the researchers.

In *Pharmacological Reviews* (2004;56: 163-184), Allan J. McLean, MD, director, National Ageing Research Institute, Parkville, Australia and David G. Le Couteur, MD, professor of geriatric medicine, Centre for Education & Research on Ageing, Concord Repatriation General Hospital, University of Sydney, Australia, concluded that "adverse drug reactions and polypharmacy represent major linkages to avoidable morbidity and mortality." They noted the lack of clinical trial evidence,

adding that “the extrapolation of risk–benefit ratios from younger adults to geriatric populations is not necessarily valid.” However, the researchers revealed the frustrating dilemma in observing that advances could also “convert healthy longevity from an asset of fortunate individuals into a general social benefit.”

It is clear that the price of not having elder populations participating in the research process in adequate numbers may be compromising the quality of life of this population.

How Long Can This Gap Persist?

“We in Dundee University are certainly making a major contribution to being inclusive of older people in clinical research,” Dr. McMurdo told *CNS SeniorCare*. Still, she added, there hasn’t been a groundswell of reaction throughout the healthcare industry.

“I received a number of positive comments about the article from colleagues like me, who specialize in medicine of old age, and directly from a number of older people,” said Dr. McMurdo. “The piece also resulted in invitations to write three further articles. Perhaps the interest in such research, expressed across so many periodicals, is a good indication toward the healthcare community taking corrective action against this problem.”

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