The evolution of clinical trials: inclusion and representation

Editorial

Éditorial

Paula A. Rochon, MD, MPH; Philip B. Berger, MD; Michael Gordon, MD

Dr. Rochon is a Scientist with the Kunin–Lunenfeld Applied Research Unit, Baycrest Centre for Geriatric Care, Adjunct Scientist with the Institute for Clinical Evaluative Sciences, Assistant Professor in the Departments of Medicine and Public Health Sciences, and core faculty member in the Clinical Epidemiology and Health Care Research Program, University of Toronto, Toronto, Ont. Dr. Berger is Medical Director of the Inner City Health Program, Chief of the Department of Family and Community Medicine, St. Michael's Hospital, and Assistant Professor in the Department of Medicine, University of Toronto, Toronto, Ont. Dr. Gordon is Vice-President of Medical Services and Head of Geriatrics and Internal Medicine at Baycrest Centre for Geriatric Care, Head of the Division of Geriatrics, Mount Sinai Hospital, a member of the Joint Centre for Bioethics, University of Toronto, and Professor of Medicine, University of Toronto, Toronto, Ont.

CMAJ 1998;159:1373-4

See related article page 1359

The underrepresentation of women, elderly people, the poor and other marginalized groups in clinical trials limits the benefit of drug therapy in these populations. People who differ because of sex, biologic factors, and ethnic and cultural factors may well have different clinical outcomes. Recent mandates to include women in clinical trials have received considerable public attention but have had questionable influence on improving the quality of information from clinical trials.[1] The first step to learning more about women's and other groups' responses to drug therapies is simple: include the groups in trials. The second and more complex step is to ensure that, when marginalized groups are included, they represent the full spectrum of the population targeted to receive the therapy. The ultimate goal of this process is to learn how to prescribe drug therapy safely for the patient groups who will be receiving them.

Since its beginning, the AIDS epidemic has highlighted inequities in Canada's social, economic and health care systems. The demographic characteristics of subjects in many AIDS trials do not match those of the HIV-infected population in terms of sex, race, economic background and risk category. For example, in Canada AIDS was once considered a disease of men, but now an estimated 21% of new cases of HIV infection are in women. The AIDS epidemic illustrates issues related to the inclusion and representation of nontraditional groups in clinical drug trials.

In this issue (page 1359) Dr. Catherine Hankins and associates evaluate participation in clinical trials by HIV-positive women enrolled in the Canadian Women's HIV Study. Of this cohort, 23% participated in an HIV clinical trial, suggesting that HIV-positive women are being included in clinical research. Their finding that women who did not finish high school, are non-white or are not receiving antiretroviral therapy were underrepresented among the trial participants suggests that the goal of achieving representation of women in HIV research remains a challenge. It is regrettable that, because of ethics restraints, Hankins and colleagues were unable to characterize the women who chose not to enrol in the Canadian Women's HIV Study cohort. The absence of information on nonparticipants makes it impossible to know the true breadth of recruitment bias in Canadian AIDS clinical trials. A detailed description is needed of the demographic characteristics of eligible and screened subjects in addition to actual study subjects in order to determine whether recruitment methods for a clinical trial are inclusive of minority or socially disadvantaged groups.[2]

One of the best illustrations of the lack of inclusion and representation of target populations in drug trials is the common practice of excluding elderly subjects. This group, the most rapidly growing segment of the population, is often underrepresented in research.[3] For example, NSAIDs are commonly used in elderly people because of the high prevalence of musculoskeletal disorders, especially in women. However, in the major drug trials evaluating NSAIDs, only 2.1% of patients were 65 years of age or over and less than 0.1% were over 75.[4] In practice, elderly people are among the largest users of drugs and have the highest incidence of serious drug-related side effects.

Elderly people who are included in clinical trials are generally younger, fitter

and predominantly male. The inclusion of older, frailer individuals in drug trials presents researchers with challenges, including the increased likelihood that these patients may be unable to complete the trial because of unwanted drug-related complications or death.[3] But it is the frail elderly who are commonly given the drugs in question.

Even in a recent drug trial focusing on a geriatric condition (donepezil therapy for Alzheimer's disease),[5] any of the patients included were younger (65 to 74 years) and without many comorbid conditions common in this population. Because of dementia's devastating effects and the hopeful reports about donepezil, in practice frail elderly people of advanced age and with a range of medical conditions will likely receive the drug in the absence of contradictory clinical trial data. If frail older patients are going to be targeted for dementia therapy we need to study this group in clinical trials to ensure the safe administration of the drug.

Recruiting nontraditional groups to participate in clinical trials can prove challenging. Strategies now being implemented to connect HIV-infected people in marginalized groups to HIV risk reduction programs and research could be applied to clinical trials in general. For example, intravenous drug users who function as peer recruiters in a system known as "network sampling" have been found to be more effective than professional community outreach workers in reaching intravenous drug users.[6] The notion of peer recruitment could be incorporated into any clinical trial being conducted in communities where large numbers of immigrants, aboriginal people or visible minorities reside. In addition, researchers could consider seeking the advice and participation of community groups and local opinion leaders.[7] Clinical trials that might appear controversial or in which recruitment problems are anticipated could benefit from the credibility and promotion of local community organizations. Researchers trying to attract nontraditional groups into their trials could also learn from strategies successfully used to recruit homeless people with serious mental illnesses into clinical trials.[8]

Obtaining adequate information about marginalized groups from any one clinical trial may remain a challenge. For example, elderly people tend to be frail and, compared with younger people, may have adverse drug effects that necessitate study discontinuation; homeless people have no fixed address and therefore are more difficult to track than other people; and prostitutes with HIV infection may have more pressing problems than wanting to participate in a clinical trial. Undoubtedly, it will require greater effort and cost to recruit and keep hard-to-reach groups in clinical trials, but these steps must be taken. Even if only small numbers of frail elderly people, homeless people or others in marginalized groups are included in each clinical trial, the data can be pooled using systematic reviews to provide better information to practitioners on potential adverse effects that may lead to safer prescribing.

Lessons from the AIDS epidemic may help researchers in other fields deal with the need to include all at-risk populations in clinical trials. AIDS research now includes women and, through the use of creative strategies, is working toward comprehensive representation of women and other underrepresented groups in clinical trials.

References

1. Rochon PA, Clark JP, Binns MA, Patel V, Gurwitz JH. Reporting of gender-related information in clinical trials of drug therapy for myocardial infarction. *CMAJ* 1998;159(4):321-7.
2. Ness RB, Nelson DB, Kumanyika SK. Evaluating minority recruitment into clinical studies: How good are the data? *Ann Epidemiol* 1997;7(7):472-8.
3. Cameron HJ, Williams BO. Clinical trials in the elderly: Should we do more? *Drugs Aging* 1996;9(5):307-10.
4. Rochon PA, Fortin PR, Dear KBG, Minaker KL, Chalmers TC. Reporting of age data in clinical trials of arthritis: deficiencies and solutions. *Arch Intern Med* 1993;153(2):243-8.
5. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, Group DS. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998;50(1):136-45.
6. Madray H, Broadhead RS, Heckathorn DD, Mills RJ. Targeted versus network sampling for accessing injection drug users [abstract 24174]. 12th World AIDS Conference. 1998 June 28–July 3; Geneva.
7. Wright J. Asking for community assistance to prepare for large HIV vaccine trials in San Francisco [abstract 24215]. 12th World AIDS Conference. 1998 June 28–July 3; Geneva.
8. Hough RL, Tarke H, Renker V, Shields P, Glatstein J. Recruitment and retention of homeless mentally ill participants in research. *J Consult Clin Psychol* 1996;64(5):881-91.

Correspondence to: *Dr. Paula A. Rochon, Baycrest Centre for Geriatric Care, 3560 Bathurst St., North York ON M6A 2E1; paula.rochon@utoronto.ca*