Clinical Trials: Time for Action

MEDLINE DISPLAYS 223 records in response to the keywords “cancer,” “clinical trials,” and “accrual.” Because the Google search engine captures government, corporate, and cancer organization sites in addition to publications in medical journals, it yields about 7,000 hits in response to the same terms. These journal articles, as well as general Internet sites, talk about the importance of improved accrual to clinical trial success, and the importance of clinical trials to advances in cancer treatment.

Clearly, there is no dearth of concern about what has been highlighted for years as a singular, serious problem: inadequate accrual of adult patients to clinical cancer trials. For more than two decades, this issue has been confronted, recognized, and studied. The dependence of therapeutic progress on improving accrual of adult patients to clinical cancer trials. For more than two decades, this issue has been confronted, recognized, and studied. The dependence of therapeutic progress on improving the stubbornly static 3% to 5% accrual rate; concern about study success, and the importance of clinical trials to advances in cancer treatment.

During its brief life (1978 to 1981) before being subsumed by another journal, Cancer Clinical Trials often grappled with why eligible patients were not accessioned to trials, and Begg et al analyzed data from six Eastern Cooperative Oncology Group (ECOG) studies, showing that elderly patients did not experience increased toxicity and therefore should be included in trials. Eight years later, Goodwin et al documented the substantial underenrollment of elderly patients in Southwest Oncology Group (SWOG) trials. Kennedy documented the poor representation of women over 65 years of age in Cancer and Leukemia Group B (CALGB) studies; his decades-long effort to render clinical trials more representative of cancer patients by age continues, joined by many others.

The most recent Annual Report to the Nation on the Status of Cancer, produced by the National Cancer Institute (NCI), the American Cancer Society, the North American Association of Central Cancer Registries, the National Institute on Aging and the Centers for Disease Control and Prevention, features “implications of age and aging on the U.S. cancer burden,” reiterating that age is the single most important risk factor for cancer. Because the population is growing and aging, a doubling of cancer incidence to 2.6 million people is expected by the year 2050, rendering the study of older patients in clinical trials more essential than ever.

Research on accrual deficiencies has continued with increasing specification, looking to explain reasons for the absence of improvement despite many years of calls for expanded participation. As reviewed by Comis et al in this issue of the Journal, investigators over the years have looked to patients for answers. Their own article, however, provides more definitive data on public perspectives. It reports the first survey of attitudes toward participation in clinical cancer trials using a national sample of adults in the United States.

Although some investigators have qualified enthusiasm for hypothetical survey questions (“if you had cancer, would you . . .”), data reported here are consistent with many other reports and, therefore, ring true. The authors found that 32% of adults are very willing to participate in a clinical trial if asked, and an additional 38% feel so inclined but have some questions or reservations. Extrapolating these data to cancer patients in the United States, they conclude that patient willingness is sufficiently broad to enable reasonable accrual to clinical trials and that the heart of the problem lies elsewhere.

Their conclusions substantiate the results of previous investigations: more clinical trials and more involved physicians are needed; comorbidities and other ineligibility requirements that minimize generalizability of results and that exclude elderly cancer patients demand reassessment; and more physicians need to be persuaded to present trial options for patients’ consideration.

It is hopefully assumed that additional clinical trials will emerge as increasing numbers of novel therapeutic agents are developed. Other issues stressed by Comis et al—ineligibility requirements and physician reluctance—appear more intractable. Insight may be gained from the strikingly different experience in pediatric oncology. Why do pediatric trials accrue the great majority of patients whereas adult trials involve a meager minority?

Fuk et al looked at eligibility criteria in a 20-year sample of National Surgical Adjuvant Breast and Bowel Program (NSABP) and Pediatric Oncology Group (POG) studies. They found that NSABP trials contained significantly more eligibility criteria than did POG studies and that numerous eligibility criteria were not necessary for high-quality studies. Their recommendations were to reduce, justify, and assess eligibility criteria. Surveys indicate that implementation of those recommendations would reduce physician reluctance to place patients on clinical trials, as protocol availability, restriction, or logistic difficulty are commonly cited by physicians as reasons for their unwillingness to attempt accrual. Examples include 1994 survey results from 1,485 ECOG investigators, 83% of whom pointed to randomization and protocol unavailability or difficulty as deterrents, and from recent studies showing similar concerns about stringent requirements and logistic barriers.

The NCI tried to deal with logistic drawbacks with its 2000 Expanded Participation Project. This effort to simplify data collection systems and otherwise encourage greater clinical trial participation by community physicians who treat 97% of cancer patients in the United States was part of a broader NCI initiative to restructure and enhance clinical trials. The Cancer Trials Support Unit, also developed by NCI and opened to cooperative group investigators in 2000, sought to improve participation by simplifying, streamlining and computerizing many functions of the process. The NCI initiatives appear to have
increased accrual to date, although more time is required for definitive results.

It is of interest to note that logistic and some other barriers cited by physicians today have edged out earlier concerns. For example, when poor accrual threatened continuation of the 1976 NSABP trial comparing segmental mastectomy with or without radiation to mastectomy alone, Taylor et al16 surveyed investigators to learn why. Concerns about negative effect on the doctor-patient relationship, discomfort with discussions about informed consent, and issues of uncertainty predominated.

Persuading physicians to broach the issue of clinical trials more often, as Comis et al8 recommend, would be greatly facilitated with resolution of today’s physician concerns, including more protocols with fewer eligibility restrictions to facilitate enrollment of additional, more representative patients. Moreover, protocols that enable physicians to discuss receipt of a promising new treatment or the best available therapy, with no placebo or no-treatment options, should also help decrease physician reluctance. Perhaps community physicians need to be reenergized through reminders of their crucial role in advancing cancer care.

In this journal in November, 1991, an editorial by Bernard Fisher17 accompanied an Illinois Cancer Center survey of oncologists’ perceived barriers to clinical trial accrual.18 On the basis of the results of that survey and his own experience with 30 NSABP randomized trials, his tone was understandably frustrated. Despite decades of prior effort, including NCI’s establishment of extensive community networks to enable most physicians and patients to participate, clinical trials still resisted reasonable accrual. The accompanying 1991 survey18 indicated that additional research should determine how to alter physician reluctance to pursue clinical trials.

In the intervening 11 years, as before, such studies have been conducted. We know the problem. It is time now, at long last, for action. Here are some suggestions: As we attempt to make clinical trials more patient friendly, increasing physician awareness also requires attention. Oncology training and relevant physician organizations should endeavor to inculcate a clinical trials ethic, making research part of the fabric of both oncology education and practice. Hopefully, this would extend the pediatric research culture to adult cancer care as well.

Because most cancer patients are treated locally, more community practitioners should be brought into the clinical trials loop. Community oncologists with special interest in research, and who contribute successfully to clinical trials, could use their expertise to train and assist colleagues. Their expertise should be recognized, as they promote research and help others to participate effectively.

While investigation, cost, and reimbursement for pharmaceutical company trials typically break even, the level of reimbursement for publicly funded research falls more than $1,500 short per patient of what is required to do the work. Increased levels of reimbursement alone are not likely to solve the problem, but greater equity would help.

Web-based efforts such as those of the NCI, the American Society of Clinical Oncology, and the Coalition of National Cancer Cooperative Groups continue to facilitate the logistics of clinical trials, and the Coalition and others are working on the issue of eligibility requirements. These efforts too should further increase patient accrual.

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REFERENCES


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