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EDITORIAL

The Study of Accrual to Clinical Trials: Can We Learn From Studying Who Enters Our Studies?

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Throughout the 1990s, less than 6% of all breast cancer patients and less than 3% of all adult cancer patients entered clinical trials in the United States.[1] At the same time, a number of well-designed, peer-reviewed clinical trials were accruing patients very slowly. The slow accrual is baffling, but even more concerning is the fact that few have studied the dynamics of clinical trials accrual in any cancer.

At first glance, there are a number of reasons why a patient should want to enter a clinical trial. Clinical trials are mechanisms for testing new cancer therapies and for providing opportunities for patients to be exposed to state-of-the-art treatments.[2] For the eligible patient, a cooperative group clinical trial and many cancer center-sponsored studies offer the patient a second or third opinion, as it is designed by a group of experts and is peer-reviewed. Unlike most cancer therapies, treatment in a clinical trial is given under conditions that are often audited, to assure it was given correctly. In contrast to adults, a high proportion of eligible children under 12 years of age are entered onto pediatric cancer studies.[3]

In this issue of the *Journal of Clinical Oncology*, Simon et al[2] study the dynamics of accrual in a single institution. The proportion of eligible patients who refused entry was significant, as was the proportion of patients who did not have a clinical trial available or otherwise did not qualify for study. The high number who did not have a protocol available or did not qualify may have been because of the lack of good scientific questions to ask at the time. It may also be that we are asking the wrong questions. This finding suggests that we who design clinical trials ought to carefully think about the importance and relevance of the questions we ask.

As part of its efforts to overcome health disparities, the National Institutes of Health has emphasized recruitment of blacks and other minorities to clinical trials. Simon et al[2] found that minorities with cancer were less likely to have a clinical trial available for their disease and stage of disease, and were less likely to be eligible when a trial was available. A most important finding is that there is a very similar proportion of eligible black and white patients entering clinical trials. This is consistent with the findings in National Cancer Institute– (NCI–) sponsored studies of the Minority-Based Community Clinical Oncology Program in the early to mid-1990s, which is a tribute to the physicians and other health care providers in this study.[4] Racially proportionate accrual is possible and it is likely as a result of health care providers having a good rapport with their patients and trust in the community in the institution as a source of good service.

Some have advocated clinical trials participation as a way of decreasing racial and ethnic health disparities. It is this physician's opinion that this is a false promise. The reasons for advocating minority participation in clinical trials are often misstated, and the ability of clinical trials to directly change dire health statistics is overstated.

The National Institutes of Health Revitalization Act of 1993 actually mandated minority inclusion in clinical trials such that subset analyses can be done to distinguish an intervention's differences among people of different races and sexes.[5] The preamble of this legislation attributes many of the disparities in health between blacks and whites to a failure to understand differences in drug activity among racial groups. The legislation is related to the belief that a clinical trials population mirroring the population at large will allow for generalization of results. The legislation was so controversial that an entire issue of *Controlled Clinical Trials* was devoted to it.[6]

This belief ignores the real and difficult problems in health disparities research. Many have documented racial differences in the receipt of cancer treatment.[7] In the case of breast cancer, many have noted that poor or minority women tend to get less than optimal therapy for their disease, including surgery, chemotherapy, or radiation. For many black patients, it is not that the drugs do not work; it

is that blacks are less likely to get optimal treatment. Indeed, several institutions have demonstrated that equal treatment yields equal outcome among patients, regardless of race.[8,9]

There is a true need to carefully define the real questions in health disparities and carefully study them. It is of note that black women in the Simon et al[2] study were more likely to have poor performance status and inadequate organ function. If the black-white disparity is to be truly addressed, the reasons for this very common finding must be explored.

There are good reasons for all cancer patients to seek participation in well-designed clinical treatment trials and to seek care from those who offer clinical trials. Warnecke et al[4,10] have suggested that those physicians who participate in clinical trials take better care of all of their patients, and not just those on trials. It is unclear if this is because participation in the protocol is a form of continuing medical education, or if better clinicians are drawn to clinical trials participation. Both may be true.

Widespread access to clinical trials and racial and ethnic proportionality is less a matter of scientific necessity than of social justice. In the early- to mid-1990s, there was racial and ethnic proportionality in accrual to NCI-sponsored treatment trials. The promotion of clinical trials over the past several years has led to a 20% increase in the number of individuals admitted to NCI-sponsored trials. The number of minorities entering trials (Asian, black, Hispanic, and Native American) has remained relatively stable while enrollment of whites has increased.[11] Patients from higher socioeconomic areas of the country are leading this increase in accrual.[1,12]

Much interest in the racial mix of clinical trials participants is as a result of a desire for the generalizability of findings. This is a misperception of the basic nature and power of the vast majority of clinical trials we conduct. Cancer clinical trials are usually developed to answer questions of efficacy and not questions of effectiveness. Efficacy means, "Does Intervention A work better than Intervention B?" Effectiveness assesses the outcomes of a treatment when applied to a large population. Effectiveness studies are usually very large and very long-term. Even the large-scale Breast Cancer Prevention Trial was designed to address efficacy: "Does tamoxifen therapy prevent breast cancer in high-risk women?"[13]

It should be mentioned that the dynamics of accrual of patients to cancer treatment trials is likely different from the accrual of healthy subjects to cancer prevention trials. Large prevention trials also tend not to accrue populations representative of the United States and can never be fully generalizable. The Breast Cancer Prevention Trial and the Prostate Cancer Prevention Trial disproportionately accrued highly educated middle and upper-middle class Americans.[13,14] Of the more than 18,000 men in the recently concluded Prostate Cancer Prevention Trial, 34.9% of the white patients and 25.4% of the black patients had postgraduate education. A cynic might say these trials attract highly-educated people who can afford to worry about preventing a problem they are unlikely to develop in the first place. Treatment trials accrue patients who have a problem and need to have it addressed.

Simon et al[2] demonstrate several important lessons through their study of accrual to breast cancer trials: 1) we who design clinical trials should think not only about the generalizability of its findings, but of the relevance, pertinence, and applicability of the question to the patients we serve; 2) we who interpret clinical trials and offer treatment to our patients must remember that many of our patients would not have qualified for the original trial; therefore, the findings may not fully apply to the whole population at risk. We should focus our decisions on objective clinical indicators such as tumor stage, grade, and receptor status, rather than race alone; 3) we who offer clinical trials must clearly explain to the public the reasons for these studies and their value to patients.

Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

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