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Editorial

Revisiting Barriers to Clinical Trials Accrual

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Properly conducted clinical trials provide high-quality evidence for a spectrum of outcomes relevant to patients, care providers, policy makers, and funders of healthcare services. Although such trials often have high internal validity, their external validity, or generalizability, depends on how representative the patients enrolled in a given trial are for the general target population. Only about 5%-8% of cancer patients participate in clinical trials, and studies conducted in the United States indicate that patients who are enrolled in trials are, on average, younger, better educated, less racially diverse, and with fewer comorbid conditions compared with typical patients with the condition of interest. These findings raise concern as to the validity of the trial-estimated treatment benefits and risks when applied in the "real world."

Improving access to trial enrollment and expanding the diversity of patients participating have long been recognized as ways to address threatened generalizability. Improved access could have other benefits such as shortened accrual times or fewer trials closing early. Forty years ago, Penchansky and Thomas (1) provided a framework describing dimensions of access: availability, accessibility, accommodation, affordability, and acceptability. Thirty years ago, Gotay (2) reviewed the available literature on barriers to trial accrual and found that nonparticipation was influenced by trial, physician, and patient-related variables. In 2010, the US National Cancer Institute and American Society for Clinical Oncology cosponsored a symposium to examine the state of science related to barriers to accrual and promoted the development of new interventions to facilitate clinical trial enrollment (3). More recently, Unger et al. (4) reviewed studies of the trial decision-making pathway and estimated that structural and clinical barriers combine to make trial participation unachievable for more than 75% of cancer patients. These reviews, among others, consistently identify both patient decision-making factors (ie, those influencing a patient accepting trial participation) and system or structural or clinician factors (those influencing if a patient has the opportunity to choose) as barriers to accrual. To what extent does each of these domains limit trial participation, and where are the greatest opportunities to overcome barriers?

In this issue of the Journal, Unger and colleagues (5) address these issues by posing the question, "What is the rate of trial participation among patients who are actually offered an opportunity to participate?" To seek the answer, they reviewed 35 research studies that individually asked this same question in a variety of clinical contexts, all in the United States. The authors then applied meta-analytical techniques to pool the findings of these individual studies and calculated the best estimate of the proportion of cancer patients who would accept enrollment on a randomized clinical trial if given the opportunity. They found that more than half of the patients in these pooled studies were willing to participate (55.0% among the 30 studies examining participation in clinical trials of cancer treatment and 55.3% in the 5 cancer control trial studies). Willingness to participate was slightly higher overall in patients receiving care in academic centers compared with those in community centers but did not differ statistically significantly between Black, Hispanic, or Asian vs White patient groups in the studies examining these factors.

This estimated proportion of more than half of patients willing to participate is in stark contrast to the estimated 5% of patients actually participating in trials. Did the meta-analysis itself have internal validity? The study used appropriate methods that adhered to PRISMA (6) methodologic recommendations, including a comprehensive search strategy for candidate studies, clear inclusion and exclusion criteria, and independent abstractions of study findings. The statistical analyses were appropriately selected and explicitly tested if factors such as a requirement for patient consent (on the enrollment study), community vs academic setting, or patient race and ethnicity group were associated with the estimated proportion of patients willing to participate. Sensitivity analyses were conducted to test the robustness of the pooled findings, and the potential for publication bias was addressed. In sum, the research would appear to be of very high quality, and the authors should be commended on their efforts.

Are the study findings generalizable? Unlike most meta-analyses in oncology that provide the best estimate of therapeutic efficacy in a narrow patient population, this analysis

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estimated an overall patient clinical trial acceptance rate across a broad range of cancer types and clinical trial interventions. The included studies had considerable heterogeneity (hence, a random-effects approach was used). Moreover, although study quality could not be formally assessed, many were retrospectively conducted. It is remarkable, however, that despite these limitations, the variation in patient acceptance rates across studies was fairly narrow (95% confidence interval ranged from 50% to 60%), and the sensitivity analyses showed the estimates to be robust.

These findings suggest that across a range of clinical trial contexts, the proportion of patients willing to accept a trial, if offered, is more than half. Could it be higher still? Several reviews have focused on patients' willingness to participate in trials. The current literature synthesis (5) found that about 1 patient in 4 cited treatment choice–related reasons (eg, a strong treatment preference) and a similar proportion expressed lack of interest, whereas fewer than 1 patient in 12 cited each of treatment toxicity, financial concerns, travel distance, or participation in an experiment to be a reason for declining. Collectively, these reasons account for about 7 out of 10 patients' preferences, but the heterogeneous nature of patients' concerns underscores the complexity of the problem and the lack of simple solutions. A focus on modifiable factors, improved understanding of patients' perspectives, and greater engagement of patient stakeholders in codesigning trials to include appealing elements and outcomes offers a promising pathway to both greater accessibility and higher rates of patient participation once offered (7,8).

Importantly, the finding of a 50% acceptance estimate, in the context of an overall trial enrollment rate of 5%, implies that only about 10% of cancer patients are given a trial enrollment opportunity. Even if patient acceptance rates climb higher, participation rates on trials would remain less than 10%. Thus, the system-related and physician-related barriers described in systematic reviews dominate the problem of low participation by limiting access opportunities for patients. These barriers are clearly relevant to the majority of cancer patients. Further, the finding that patient acceptance rates varied little among racial and ethnic groups implies that observed disparities in clinical trial participation arise predominantly from system and/or clinical barriers rather than from patient decision-making. Progress is being made in addressing these barriers such as the US Food and Drug Administration draft guidance documents on broadening trial inclusion criteria, new applications of social media (9), development of clinical trial research networks (10), and greater engagement of patient stakeholders to design trials that matter most to both clinicians and patients (7), among others (3). Changes in practice (such as virtual patient management) owing to COVID-19 considerations may also provide new opportunities to improve access. Novel approaches to improved accessibility continue to be required and should be designed to test hypotheses based on modifiable mechanisms by which common barriers prevent patient access to trials.

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Data Availability

Not applicable.

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