The conduct of clinical trials is vital for discovering new cancer treatments. The success of trial findings in changing clinical practice is predicated on numerous factors, including the extent to which the trial cohort is representative of patients anticipated to receive a new experimental therapy. In this context, it is useful to envision a more ideal, demographically and socioeconomically open and inclusive clinical trial system. In such a system, enrollment would be readily and equitably available, such that trial cohorts would better approximate a random sample of the US population, even in the presence of extant differences in underlying health status between populations. For patients, for whom participation in clinical trials often represents an opportunity to receive the newest treatments, such a system would be free of the structural and patient barriers that have been routinely identified. Such a system would also build greater confidence that trial findings are widely applicable, likely encouraging more rapid uptake of new treatments in practice.

Instead, the clinical trial system in the United States is beset with systemic structural, clinical, physician, and patient barriers, generating clinical trial cohorts that are distinctly nonrepresentative. Studies have repeatedly, over decades, demonstrated that patients in clinical trials are much younger than their nonparticipating counterparts. In 2000, the Centers for Medicare & Medicaid Services required that Medicare cover the routine care costs of clinical trials so that Medicare patients interested in participating in trials could do so more easily. However, the proportion of patients aged 65 years or older enrolling to clinical trials has increased only modestly, remaining approximately between 30% and 35%, even as nearly 2 of 3 patients with cancer are 65 years or older. Representative enrollment of some racial and ethnic minority groups has also been lacking. A recent study by Loree et al highlighted the issue. Among trials leading to US Food and Drug Administration (FDA) approvals for new cancer drugs, the enrollment of Black patients was only 22% of the expected rate based on US cancer population incidence. This dramatic disparity was subsequently shown to be primarily evident in pharmaceutical company sponsored trials, rather than National Cancer Institute (NCI)-sponsored trials, with Black patients representing 12.1% of the US cancer population, compared with 9.0% for NCI-sponsored trials but only 2.9% for pharmaceutical company–sponsored trials. This discrepancy is likely due to different recruitment strategies. Whereas pharmaceutical companies—whose mission is directly tied to winning approval of new drugs—primarily conduct their trials at large academic centers and, often, at international sites, NCI-sponsored trials are conducted with a concerted outreach to community, minority, and underserved sites, with an emphasis on improving representativeness of minority and rural populations. Perhaps not surprisingly, enrollment representativeness for racial groups in NCI-sponsored trials is often more in line with cancer population rates.

These demonstrated disparities in the clinical trial system sometimes seem to have calcified. And indeed, in the study by Varma et al, the authors have filled another key research gap, showing that disparities in enrollment of older patients and Black patients persist throughout the evaluation process of novel cancer therapeutics by the FDA. In fact, the magnitude of the underrepresentation barely changed between premarketing and postmarketing study settings. As the authors argue, adequate representation of demographic subgroups in both study settings is necessary to understand the safety and efficacy of new drugs.
The FDA recognizes the crucial role of representativeness in trials for new drug approvals and has recently taken steps to address this issue. In a workshop jointly convened by the FDA and the American Association for Cancer Research, stakeholders from across the clinical cancer research spectrum sought to identify strategies to improve representativeness of Black patients in FDA trials for multiple myeloma, a disease that occurs commonly in Black patients. Among the proposals were the prospective targeting of specific treating institutions serving diverse populations and the use of real-world data to augment what is learned from trials to fill gaps in knowledge about patient subpopulations. The working group also recommended that the conduct of postapproval trials with more inclusive eligibility criteria would better enable identification of safety issues for certain subgroups. However, the findings from Varma et al suggest that postmarketing studies—even if designed to be more inclusive—still fail to adequately represent the demographic profile of the US cancer population. If so, the conduct of postmarketing trials may have limited utility in resolving the lack of data on diverse populations in premarketing trials.

The FDA recently issued draft guidance regarding the inclusion of older adults in cancer clinical trials, and the NCI is currently planning a workshop for April 2021 to focus on the challenges of and opportunities for engaging older adult patients with cancer in the NCI clinical trials network. Clinical trial eligibility criteria are designed in part to maintain patient safety by excluding patients less likely to tolerate experimental therapy. Thus, patients with other concurrent illnesses, which are more common among older adults, frequently do not meet the trial eligibility criteria and are excluded for well-intentioned reasons. Therefore, it is inevitable that older patients will never account for two-thirds of patients in trials. However, recent and continued efforts to reduce unnecessary exclusion criteria are likely to improve the participation rates of older patients in trials.

Despite the inevitability of older patient underrepresentation in trials, Varma et al conclude that “the FDA should require demographic representation in premarketing and postmarketing studies that approximates the population expected to use the therapeutic.” Although the authors go on to indicate that this could be ensured through the up-front investment of sufficient resources for recruitment, therein lies the rub, as there can be no guarantee that representative enrollment across the intersecting domains of age, sex, race, and ethnicity will necessarily be achieved in a timely fashion, especially given the multidimensional layers of structural, clinical, physician, and patient barriers that exist to trial enrollment. Full representation of demographic and socioeconomic groups is clearly desirable, for reasons of patient equity and scientific inquiry. However, given the challenges of achieving this, the potential trade-offs should be considered. If fully ascribed to, the requirement to achieve fixed demographic enrollment targets could in fact delay new drug development, as trials struggle to achieve required accrual, especially among older patients. If so, this well-intentioned strategy could end up hurting the very populations it aims to help by delaying access to novel therapeutics. It is noteworthy that the FDA’s own draft guidance recommends only that trials include populations of patients intended to receive new interventions but does not indicate that full representativeness is required.

As Varma et al suggest, a prospective strategy that better targets treatment settings with diverse cancer populations will improve demographic and socioeconomic representativeness and limit the potential for harmful delays in the development of new treatments. At the same time, continued and focused efforts to eliminate structural, clinical, physician, and patient barriers to enrollment are necessary to allow patients of all backgrounds to more easily participate. By such comprehensive means, the United States may finally begin to recognize the ideal of an open, inclusive clinical trial system readily accessible to all patients with cancer.
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Conflict of Interest Disclosures: None reported.

REFERENCES