Why Diverse Clinical Trial Participation Matters

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Marginalized racial and ethnic groups, women, and other historically disenfranchised populations are substantially underrepresented in clinical trials, despite increasing concern about this issue among policymakers, patient advocates, and some industry leaders. A recent report from the National Academies of Sciences, Engineering, and Medicine (NASEM) brought additional, much-needed attention to this problem and suggested a number of reforms to the clinical research enterprise.[1] But interest and investment in efforts to improve diversity and representativeness in trials are unlikely to be sustained if the goals of diversification aren't clearly articulated and understood.

Broadly, the goals of increasing diversity in clinical trial participation include earning and building trust, promoting fairness, and generating biomedical knowledge (see table). These three goals are each valuable on their own, and accomplishing one goal might result in progress toward another. New initiatives designed to diversify clinical trials may not promote all three goals equally, however. We believe that earning trust and promoting fairness are the most important of these goals and provide the clearest opportunities for realizing value from increasing diversity and representativeness in trials.

Regarding the goal of earning trust, medical institutions have engendered mistrust through a history of research abuses and restrictions on equitable access to clinical services that continue to the present day. Among many examples, after the revelation of the abuses in the Tuskegee syphilis study, Black men were less likely to trust physicians, reduced their health care use, and had increased mortality rates.[2] For many disenfranchised groups, the persistent lack of diversity in contemporary clinical trials may exacerbate perceptions that medical research and medical institutions are exclusionary and not worthy of trust.

A recent experiment sheds light on this issue. Investigators randomly provided patients with hypertension with results from one of two trials of a new hypertension drug.[3] Both trials showed that the medication was effective at lowering blood pressure. In one trial, 15% of participants were Black; in the other trial, less than 1% were Black. Giving patients the results from the more representative trial increased by 20 percentage points the likelihood of Black patients' believing that the drug would be as effective for them as it was for the trial participants, without altering White patients' perceptions of the drug's effectiveness.

This study shows how inclusive enrollment practices can increase patients' interest and confidence in effective new treatments. Such benefits might not require a precise figure for a treatment's efficacy in a particular demographic subgroup but could arise because inclusiveness promotes perceptions that a study and its findings are legitimate. Indeed, the benefits of inclusiveness might extend beyond the particular clinical scenario being studied to include reducing medical mistrust among marginalized communities more broadly. It will be important for future research to elucidate the ways in which inclusive clinical trial practices may affect public trust. Investments in such research could help reveal which practices are most successful in promoting trust and which ones raise public concerns about exclusion or exploitation.

The second key goal of increasing diversity in clinical trials is promoting fairness. Participating in a trial can confer benefits and burdens. Fairness requires removing obstacles to participation that may disproportionately affect certain groups of people, such as recruiting only in academic medical centers, to which access may be limited among disenfranchised groups, or requiring frequent in-person visits, which poses high opportunity costs associated with participation for people with inflexible work or family circumstances. Fairness also requires making efforts to ensure that the burdens of participation are shared broadly and equitably across all members of society who stand to benefit from a study's results.

Reducing barriers by reaching potential participants using mobile recruitment strategies, providing transportation or parking vouchers, and offering robust

Goals of Increasing Diversity in Clinical Trials.

Goal	Key Challenges	Implications
Building trust in medical research and institutions	Distrust of medical and scientific professions can be an important obstacle to receiving effective medical care.	The effect on public trust of the design and conduct of clinical trials can be as important to public health as trials' results. Investments should be made in elucidating how clinical trial practices affect public trust.
Promoting fairness for potential participants and their communities	Opportunities to participate in trials are limited. Preferences, resources, and trust all affect willingness to participate in trials. Health systems' capacities to conduct trials vary among communities.	Overcoming unjust barriers to participation for disenfranchised groups will require affirmative outreach and recruitment actions. Grading trials on inclusive outreach and recruitment practices, rather than solely enrollment demographics, may better reflect recruitment equity. Investing in trial capacity in marginalized communities may benefit such communities broadly by improving adoption of innovations.
Generating biomedical knowledge	Sample sizes are often too small to permit assessment of treatment efficacy within particular subgroups. Clinically significant differences in treatment efficacy between groups that are underrepresented and those that are overrepresented in trials may not be common. Efforts to diversify trials address only some of the barriers to efficient patient recruitment.	Investigators should acknowledge that more inclusive trials may not show whether a treatment is effective for certain patient subgroups or meaningfully shift estimates of the treatment's efficacy. Shifting the focus of trials to diseases that disproportionately affect marginalized groups may more effectively generate knowledge benefiting these groups. Future meta-research could clarify the importance and detectability of heterogeneous treatment effects.

compensation and incentives could help close gaps in representation. Building inclusive trial infrastructure in underserved communities is a particularly promising step because it could not only lead to more diverse participation but also promote fairer distribution of gains in medical knowledge by accelerating the adoption of medical advances in these communities. Dedicated efforts to promote diversity in trials are therefore likely to simultaneously promote fairness.

The third goal, advancing biomedical knowledge, is a core purpose of clinical research. The recent NASEM report (one of us was on the committee that produced the report) emphasizes that increasing trial representativeness may improve the generalizability of research findings, produce new biologic insights, and yield targeted therapeutic strategies.[1] Pushing the frontier of scientific knowledge has been an important rationale for diversifying trials. But this rationale raises questions about whether and why treatment effects might differ substantially between groups that have and those that have not been underrepresented in biomedical research, the ability of trials to identify these differences in treatment effects, and whether conducting larger, more diverse trials will produce more useful knowledge than conducting more trials focused on diseases that disproportionately affect marginalized racial or ethnic groups.

Gains in biomedical knowledge associated with increased trial diversity generally depend on the existence of heterogeneity in treatment effects among patient groups. Even if such heterogeneity exists, however, it's difficult to detect unless sample sizes are increased appreciably. In some disease areas, such sample-size increases may not be possible. In other cases, any potential gain in biomedical knowledge associated with enabling detection of heterogeneous treatment effects could come at the cost of studying average treatment effects for more interventions. As a result, the important goal of generating knowledge that benefits groups that are underrepresented in biomedical research may be better accomplished by funding more trials focused on diseases that disproportionately affect such groups than by emphasizing shifting trial participant demographics alone. Further investment in research methods could advance the statistical tools that are used to detect and correct bias resulting from unrepresentative trial samples.[4] As the research community studies these issues, however, investigators should be mindful of the scientific and ethical

gaps in prior efforts to use race in medical decision making.[5]

Some scholars have argued that diversifying clinical trial participation could also speed innovation by enabling more rapid accrual. Although this effect is plausible, diversifying trial enrollment isn't required to meet target sample sizes more quickly. Other measures are likely to have a greater effect on the pace of accrual, such as reducing the use of exclusion criteria, leveraging mobile technologies to reach potential participants, providing sufficient incentives for participation, and streamlining the consent process when the risks associated with trial participation are low. In sum, we believe that — even in the absence of compelling hypotheses about heterogeneous treatment effects and statistical power to reliably detect such effects or (eventually) enough data to perform careful patient-level meta-analyses — there is still considerable value associated with diversifying trials because of potential gains in trust and fairness.

As the research community explores how to increase diversity in clinical trials, the community shouldn't lose sight of why it's important to do so. Choosing policy goals mindfully is akin to choosing a journey's destination; it helps us plan our route, measure our progress, and know when we have arrived. We believe the central goals of reforming the research process should be building trust among underserved communities and treating potential participants fairly. Although diversifying trial participation might also expand biomedical knowledge, it's essential that the promise of knowledge generation doesn't overshadow the goals of improving the trustworthiness and fairness of U.S. health care. These latter goals are foundational to effective physician–patient interactions and to facilitating the generation and dissemination of biomedical knowledge. Alongside broader reforms addressing systemic inequities in access to care and reimbursement for services, creating an evidence base built on studies with diverse populations is crucial to mitigate the profound inequalities in health outcomes that have only widened during the Covid-19 pandemic.

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