

How close are we from achieving demographic diversity in clinical trials? Insights from Singapore

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Clinical trials are essential for assessing the efficacy and safety of new therapies. Because different patient subgroups may respond variably to treatments, it is important to emphasise diversity among participants. This approach ensures that the trial population accurately reflects the patients who will use the medication in real-world settings and helps generate broadly applicable evidence. Over half a century after Archie L. Cochrane's call for robust, impactful and equitable trials,¹ external validity remains a significant concern for clinicians when applying clinical trial results.

Results from clinical trials may not be universally applicable due to distorted demographic representativeness caused by trial recruitment criteria. Recent studies highlight this issue: for 302 cancer trials with 262,354 participants from the US conducted between 1994 and 2015, the median age of trial participants was on average 6.47 years smaller than the population median age for the disease site.² In 122 COVID-19 trials with 176,654 US participants, female representation was 48.9% in prevention trials and 44.6% in treatment trials, compared to 52.4%³ in the general US population. Among 213 Pfizer-funded trials with 103,103 US participants conducted between 2011 and 2020, Asian participants exceeded census levels in 16.0% of trials, Native Hawaiian and Pacific Islander participants in 14.2%, and American Indian and Alaska Native participants in only 8.5% of trials.⁴ The lack of diversity in clinical trials—manifested in age, sex and ethnic disparities—has long been considered a moral, scientific and medical issue that hinders innovation and accessibility.⁵

Singapore is renowned for its long-term commitment to fostering an inclusive society for its 4 major ethnic groups: Chinese, Malay, Indian and Others. Due to its island city-state nature, Singaporean participants are frequently involved in multiregional clinical trials. This issue of the *Annals* features one of the first systematic review that comprehensively examines the representativeness of participants in pharmaceutical randomised controlled trials conducted in Singapore. This review not only

enhances our understanding of local clinical trials, but also highlights the importance of diversity representation in multiregional clinical trials.⁶

After reviewing 23 trials involving Singaporean adult participants conducted between 2017 and 2022, Bin WJJ et al. found that women, ethnic minorities and elder individuals were underrepresented.⁶ It is crucial to prioritise the inclusion of women, minorities and the elderly when recruiting participants in Singapore, as is recommended in other countries.⁷ Despite nearly half of the Singapore-only studies meeting census criteria for ethnic diversity, over one-third of trials did not fully disclose ethnic information. Most trials failed to detail recruitment strategies, analyse demographic representativeness and external validity, similar to issues observed in the US.⁹ Inadequate demographic representation and insufficient reporting hinder the development of robust, impactful and equitable clinical trials. Furthermore, only one multiregional study provided details beyond the umbrella term “Asian”, which suggests homogeneity and overlooks interethnic differences that can affect drug responses.⁸ This ambiguity in reporting results from multiregional clinical trials exacerbates the challenges faced by minorities living in small-to-medium-sized countries.

Since the turn of the millennium, demographic diversity in pharmaceutical clinical trials has steadily increased, especially in the US.⁷ Historically, women of childbearing potential were excluded from Phase 1 and early Phase 2 research due to the risks associated with thalidomide use during pregnancy.¹⁰ This restriction was lifted by the US Food and Drug Administration guidelines,¹¹ but even today, women of childbearing potential remain underrepresented in early-phase clinical trials compared to late-phase trials, reflecting remnants of these earlier regulations.¹² Governmental regulations significantly impact demographic diversity in clinical trials, highlighting the importance of regular updates. The National Institutes of Health Revitalization Act has been continuously updated to improve the inclusion of women and minorities in clinical

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trials, requiring inclusion in all biomedical research projects and clarifying reporting guidance,¹³ revising minimum standards of inclusion¹⁴ and mandating disclosure on ClinicalTrials.gov.¹³

Despite regulatory advancements, minorities remain underrepresented in clinical trials compared to their proportions in the US populations.⁹ In the US and globally, the pharmaceutical industry plays a key role in applied preclinical and clinical research, as well as in the production, marketing and distribution of new therapies.¹⁵ Industry-funded trials have been shown to be associated with greater age disparities, unlike government initiatives.² This raises concerns among researchers that regulatory and financial incentives might indirectly reward homogeneity, reducing confounding risks due to patient-related factors, and resulting in a higher enrolment of White individuals.^{9,12} Investigating demographic disparities among trial participants due to industry funding is crucial, especially given past concerns that industry sponsorship could introduce bias in result reporting.¹⁶

Beyond our critique of governments and the industry, we acknowledge the social factors contributing to the disparities. These include, but are not limited to, the accessibility of trial sites, leading to age disparities;² reduced willingness to participate, differences in prognosis, perceived symptoms and perceived greater risk of harm from interventions, resulting in gender disparities; and the location of trial sites, institutional and/or systematic racism, distrust of healthcare systems, low socioeconomic status and language and communication barriers, causing ethnical disparities.³ Effective solutions that resonated with both participants and the healthcare system often involve active community engagement, thoughtful logistics planning and clear communication of the research process.¹⁷ A significant barrier to diversifying participation among principal investigators, coordinators or site staff is the lack of demographic competency.¹⁷ From a technical standpoint, failing to recognise demographic diversity can invalidate clinical trial outcomes. For instance, when a disease is more prevalent among elderly individuals, relying solely on census data for trial enrolment may be inadequate;¹² epidemiological data could serve as a more appropriate reference.

After analysing the current study populations in Singapore, the authors suggest that special attention should be given to female participants and individuals of Indian ethnicity.⁶ Increasing transparency at each recruitment stage is also

necessary to facilitate the assessment of bias and the determination of generalisability. For Singapore and multicultural societies, we recommend the following:

- Governments should lead in refining regulations and tailoring reporting formats for demographic diversity by thoroughly investigating the real-world issues faced by the underrepresented groups and frequently updating relevant policies.
- The industry, as the primary implementer of clinical trials, should take on more responsibility to help achieve equity.
- Communities serving as the mediator between patients and the healthcare system should excel in creating an environment of trust and facilitating effective communication.
- Trialists should consider the actual demographic diversity in their studies, taking disease prevalence into account for certain conditions.

To achieve the United Nations Sustainable Development Goal 3,¹⁸ “ensure healthy lives and promote well-being for all at all ages”, international collaborations are needed to establish regulatory guidelines for multiregional clinical trials that safeguard the well-being of minorities in small-to-medium-sized countries.

Trial participants should ideally reflect the diverse population that will receive the treatment. A robust, impactful and equitable clinical trial must ensure that safety and efficacy outcomes reliably indicate the investigational treatment’s benefit-risk profile for general use. Embracing demographic diversity and collaboratively dismantling barriers are crucial steps towards a future where no one is left behind.

Declaration

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