nature reviews drug discovery

nature > nature reviews drug discovery > comment > article

COMMENT | 08 May 2024

First, do no harm: a global perspective on diversity and inclusion in clinical trials

New requirements for clinical trial sponsors to submit diversity action plans to the US Food and Drug Administration (FDA) are an important step to embed planning for diverse representation in clinical trial research. These must not, however, be implemented in ways that are detrimental to other countries' health and research interests.

By Katharine Wright, Willyanne DeCormier Plosky, Hayat R. Ahmed, Sarah A. White & Barbara E. Bierer

Introduction

Diversity in clinical trial enrolment is increasingly recognized as essential for both ethical and scientific reasons[1]. Inclusive approaches to research participation help to ensure that research is alert to, and responds to, the needs of all sectors of society. In

maximizes the opportunity to detect important signals of variability. Such signals can then be pursued in further studies or through subsequent use of real-world evidence.

The need for diversity in clinical trial participation is now recognized in US law. The Food and Drug Omnibus Reform Act 2022 (FDORA) requires clinical trial sponsors seeking US marketing approval for their products to submit "diversity action plans" for many clinical trials, including phase III studies of new drugs and pivotal studies of interventional devices. Under the same statutory authority, the FDA is required to issue guidance within a year on the format and content of such plans "pertaining to the sponsor's goals for clinical study enrolment, disaggregated by age group, sex, race, geographic location, socioeconomic status, and ethnicity." Sponsors are not only required to set out their enrolment goals in a format to be specified by the FDA, but also to explain their rationale for selecting them and their plans for achieving them. Thinking about diverse recruitment to clinical trials will no longer be a matter of discretion or good practice: for those seeking access to US markets, it will become legally mandated. But how will this affect studies conducted in other countries, as part of multi-regional clinical trials?

Diversity in clinical trial participation in a global context

While the current focus on diversity and representation in clinical trial participation generally relates to trials conducted within individual jurisdictions, the same issues arise even more starkly in research conducted on a global scale. Epidemiology, research priorities and causes of social or economic exclusion differ between countries and regions, and so each jurisdiction may require a different approach if the goals of diverse, inclusive and equitable participation in research are to be achieved for different

and whether the primary aim is social justice for US and/or non-US populations, scientific relevance, or both.

Some categorizations used in seeking more diverse participation in clinical trials, such as age, biological sex or comorbidities, relate to factors that may directly influence differential outcomes in a study. These categories generally remain meaningful if aggregated across study sites from a number of different countries. Other categorizations, in particular population descriptors such as race, ethnicity or ancestry, may be valuable for social justice reasons, so that people can identify with those involved in a study and have access to potentially beneficial treatments. The scientific value of these descriptors, however, is increasingly contested, and they may now primarily have some relevance as proxies for socio-economic disadvantages and discrimination that are strongly associated with ill-health, that are implicated in variable responses to some medications (for example, relating to poor diet, stress or inability to maintain treatment regimens) or that affect access to healthcare and to participation in research[4]. If relevant and culturally sensitive, such descriptors may still be used as a tool to help include underserved and marginalized populations in the research, but they remain social constructs and not intrinsic factors correlating, for example, with genetic diversity[5]. Nor do they translate readily between countries and regions, both because the categorizations differ by region and because socio-economic disadvantages and exclusion from research can have very different drivers in different contexts.

These factors create significant challenges when seeking to address questions of diversity in clinical trials conducted across multiple different countries. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals

question of how trials can be conducted across world regions in ways that most effectively meet differing regulatory requirements, thus minimizing the need for expensive and lengthy repeated trials. However, neither of these guidelines directly addresses questions of diversity within countries, or the inherent difficulty of aggregating data based on categorizations that are only meaningful in context.

Implications beyond the USA

The FDA should be commended for its attention to clinical trial diversity. Its policy decisions are appropriately centred on the needs and interests of those living and accessing healthcare in the USA. However, clinical trials are conducted across multiple countries and regions, in accordance with ICH E17, to generate the evidence necessary to meet the efficacy and safety requirements of multiple national or regional regulatory authorities efficiently. This raises several challenging questions. If diversity action plans are predicated on the epidemiology of particular diseases in relation to the demography of the USA, what will this mean for the needs and interests of populations elsewhere in the world? Will the development of FDA-mandated plans lead to increased enrolment of participants in other countries who are perceived to fit US categories (such as the racial and ethnic categories specified by the US Office of Management and Budget (OMB)) regardless of relevance, benefit, or risk of exploitation to those participants? What will this mean with respect to attention to 'diversity' and equitable access to clinical trials in countries outside the US — or, indeed, to equitable access within the US? Enrolling participants in Africa who would be categorized as Black, or in Latin America who would be categorized as Hispanic, for example, does not contribute to the goal of achieving better inclusion of African or Hispanic Americans within the USA. The FDA has not yet clarified whether and how it will consider global versus US demographic representation

to the FDA mandate to diversify clinical trials in the USA, the recruitment of participants in other countries occurs with reference to their own needs and interests. The OMB categories for race and ethnicity may help ensure that populations routinely underserved in the USA are identified and included in research within the USA, but there is nothing to suggest that they have that same resonance in other countries. These categories neither reflect the ethnic or cultural makeup of other countries nor necessarily have the same associations with social, economic and environmental factors that may directly impact the safety, efficacy or use of the study intervention. In addition to ethical concerns about recruitment practices that may be difficult to justify within the country where they are taking place, what practical value will such demographic data provide once aggregated and out of context?

These challenges are not insoluble. It is possible for those making operational decisions on country and site selection to address the needs of underserved populations in other countries at the same time as meeting US regulatory expectations — for example, by addressing barriers to diverse recruitment in other settings, including with reference to post-trial access to effective interventions. Site selection should follow purposeful engagement in the local and regional culture, considering the needs of the local population, and proceed only if the trial is responsive to those needs. Criteria for site selection should be explicit, documented and consistent with a sustained commitment to the region and country.

It seems highly likely that other jurisdictions will, in due course, adopt a similar approach to the FDA in mandating diversity action plans that consider the demographics and health requirements of their own populations when enrolling

and responding to the complexities of diverse enrolment in the context of multi-country trials.

doi: https://doi.org/10.1038/d41573-024-00078-4

References

1. Schwartz, A. L., Alsan, M., Morris, A. A. & Halpern, S. D. Why diverse clinical trial participation matters. *N. Engl. J. Med.* **388**, 1252–1254 (2023).

2. Peters, U. et al. Considerations for embedding inclusive research principles in the design and execution of clinical trials. *Ther. Innov. Regul. Sci.* **57**, 186–195 (2023).

3. Castellon-Lopez, Y. et al. A community-partnered approach for diversity in COVID-19 vaccine clinical trials. *J. Clin. Transl Sci.* **7**, e23 (2022).

4. Ioannidis, J. P. A., Powe, N. R. & Yancy, C. Recalibrating the use of race in medical research. *JAMA* **325**, 623–624 (2021).

5. National Academies of Sciences, Engineering, and Medicine. *Using Population Descriptors in Genetics and Genomics Research: A New Framework for an Evolving Field* (The National Academies Press, 2023).

COMPETING INTERESTS

The authors declare no competing interests.

Nature Reviews Drug Discovery (*Nat Rev Drug Discov*) | ISSN 1474-1784 (online) | ISSN 1474-1776 (print)