Population diversity in clinical trials for rare diseases:

A regulatory writer's perspective

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doi: 10.56012/chhh9584

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Abstract

Ensuring population diversity in clinical trials is essential yet challenging and increasingly complex in the rare disease landscape. The unique challenges in clinical development for rare diseases include limited medical and scientific knowledge, poorly understood natural history data, sample size constraints, and a lack of drug development experience. This article will discuss the evolving regulatory framework for encouraging diversity in clinical trials, explore the unique challenges of applying recommendations within the rare disease landscape, and highlight sustainable solutions for overcoming challenges.

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Introduction

Clinical trials are essential to determine whether a medicinal product (hereafter referred to as "drug") works and is safe. Individuals may show varying responses to drugs due to a combination of intrinsic and extrinsic factors. Therefore, it is a regulatory requirement that sponsors of clinical trials assess for unusually large or small responses in population subgroups, for example, examining whether there are any differences by age, sex, and race compared with the overall population.[1] However, historically, the population of clinical trials has been dominated by White males; marginalised racial and ethnic groups, women, and other historically disenfranchised populations have been substantially underrepresented. This makes it impossible to make a comprehensive assessment across an entire affected population who are likely to take the drug, and leaves the clinical relevance on the target population a matter for post-marketing activities.[2] One such case occurred in 2013 when the FDA announced that women who took zolpidem (for insomnia) were at risk for excessive daytime sedation and impaired driving proficiency following bedtime doses. Consequently, the FDA lowered the dose in women as the recommended dose was based on male participants.[3]

> Maximising the use of all available data about a new product is paramount in rare disease drug development.

Over the past few decades, regulatory guidelines on clinical trials have clearly specified that enrolled participants should be representative of the population most likely to use the drug. Nonetheless, homogenous groups continue to overshadow clinical trials, and there is little representation of other characteristics that reflect the target population. This lack of diversity has prompted the EMA and FDA to develop dedicated guidance to address this, which aims to encourage sponsors to design trials that facilitate enrolment of the target population. However, the proposed regulatory strategies have become increasingly complex to implement for many rare diseases, where small populations and unique challenges dominate.

This article will discuss the evolving regulatory framework for encouraging diversity

in clinical trials, explore the unique challenges of applying recommendations within the rare disease landscape, and highlight sustainable solutions for overcoming these challenges.

Regulatory framework

The regulations around diversity in clinical trials are evolving. The Clinical Trial Regulation No 536/2014,[4] which governs clinical trials in the EU, reinforces the requirement that participants should represent the population the drug is intended for, and has a clear emphasis on age and sex. There is an expectation that sponsors must provide a justification if a trial does not reflect the target population. However, there is no reference to race, keeping ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data[5] the primary guidance for evaluating the impact of ethnic factors. There is no expansion on considering intrinsic and extrinsic factors when designing trials, in view of the EMA adopted guidance ICH E17 Multi-Regional Clinical Trials.[6] ICH E17 recognises that differences in medical practice, diet, environmental factors, cultural or socioeconomic factors (e.g. contraceptive use, preferences for a particular route of administration), geographic location, and access to healthcare can impact trial results. These factors may also impact recruitment, compliance, and participant retention.

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The regulations in the USA have developed considerably over decades. In 2013, an FDA report to Congress highlighted demographic data gaps, which birthed the Diversity Action Plan.[7] This plan provided recommendations to standardise data collection, improve data quality and public availability, ensure demographic representation, and consider the integration of diversity throughout a drug's lifecycle.

The plan was reflected in the FDA Guideline on Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products Guidance for Industry, 2016,[8] which gives an update on a standardised approach to collecting and reporting race and ethnicity data. It recognises that "race and ethnicity categories are not anthropologically or scientifically based designations, but instead are categories that describe the sociocultural construct of our society", highlighting the importance of considering additional factors when designing trials. The significance of collecting comprehensive demographic data has been emphasised in a June 2024 revision to "Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products Guidance for Industry," to promote the inclusion of race and ethnicity information in the proposed product labelling by providing the baseline demographics of the study population in the Clinical Studies and Adverse Reactions sections.[9]

To unequivocally encourage population diversity in clinical trials, the FDA issued "Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry, 2024".[10] This guidance focuses on increasing the enrolment of underrepresented populations, underscoring the necessity of considering demographic characteristics (e.g. sex, race, ethnicity, age, location of residency) and non-demographic characteristics of populations (e.g. patients with organ dysfunction, comorbid conditions, disabilities, those at the extremes of the weight range, and populations with diseases or conditions with low prevalence). It primarily recommends broadening study eligibility criteria and using study designs to reduce participant burden to "create a study population that more accurately reflects the patients likely to take the drug if it is approved, and allow assessment of the impact of those characteristics on the safety and effectiveness of the study drug."[10]

To actively engage sponsors, the FDA issued a draft guidance titled "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies,"[11] which referred to a new document (Diversity Action Plan) that sponsors should submit to show the plan for enrolling a diverse population into certain late-stage clinical trials. While population diversity is often viewed after enrolment by evaluating the demographic and baseline characteristics of the study results, the Diversity Action Plan will ensure the following are purposely well-thought-out prior to enrolment: a. enrolment goals by race, ethnicity, sex and age, b. the rationale for enrolment goals, and c. measures to meet those goals.

However, in January 2025, days after US President Trump issued an executive order to terminate federal diversity, equity, and inclusion programs, the FDA quietly removed the draft guidance "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies" from their website. This apparent act of dismantling is concerning and raises questions about the FDA's commitment and the applicability of statutory obligations for sponsors to submit Diversity Action Plans.

Rare diseases

The EMA defines a disease as "rare" if it affects less than 5 in 10,000 people in the EU.[12] Rare diseases impact more than 400 million people worldwide, yet most conditions have no approved treatment. Clinical development in the rare disease landscape is complex as there is often limited medical and scientific knowledge, poorly understood natural history data, sample size constraints, and a lack of drug development experience.[13] Population diversity in a trial becomes increasingly challenging with the added complication of affecting only small, geographically dispersed populations.[13] However, diversity is vital to ensure results are safe and applicable to the general population.

Challenges with increasing diversity in rare disease clinical trials

Broadening eligibility criteria

> Diversity is vital to ensure results are safe and applicable to the general population.

Rare diseases are highly diverse, with varying prevalence, rates of progression, and degrees of heterogeneity that can affect both clinical manifestations and disease courses within a condition, and little is known about a disease's natural history and pathophysiology.[13] Because of this, the study eligibility criteria in clinical trials for rare diseases are often narrow to limit variability.

One of the key regulatory approaches to increasing the enrolment of a diverse population is to broaden the eligibility criteria of the clinical

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trial.[11] While this approach may satisfy an increase in diversity, broadening it too extensively could increase variability, complicating the interpretation of trial results.

Sample size

Conducting clinical trials for rare diseases is inherently challenging because of the small number of available participants. A recommended regulatory approach to increase diversity is to increase the proportional enrolment of specific populations of interest. However, this is not feasible for many rare diseases, where populations are small and enrolment is slow.

Ways to increase diversity in clinical trials for rare diseases

Adaptive trial designs

A clinical trial designed to allow prospectively planned modifications to one or more aspects of the trial based on interim results is described as having an adaptive design. Adaptive trial designs can provide a variety of advantages in the rare disease landscape as they allow adjustments to information that was not available at the start of the trial.[14]

By using an adaptive design, a trial can be planned that allows modifications to the study eligibility criteria following interim results. This flexibility could permit the inclusion of underrepresented groups who may have initially been excluded because of narrow eligibility criteria and enable the trial to reflect better the diverse population likely to take the drug.

Another adaptive approach is a study designed to prospectively plan modifications to the sample size based on interim results.[11] If certain groups are underrepresented early in the trial, and it is possible to increase the sample size considering the rarity of the disease, recruitment could target specific groups.

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Community engagement

Research has identified many barriers to the inclusion of diverse populations in clinical trials, which can be buried within the rare disease community. Participants from marginalised communities often mistrust the pharmaceutical industry, fear exploitation, lack awareness of their disease or of available trials, and have language barriers or operational constraints.[15] Concurrently, sponsors may have limited commitment and effort, conduct centralised studies, lack culturally or racially diverse staff, lack community engagement, and have negative attitudes about willingness from marginalised communities.[15]

Patient advocacy plays an instrumental role in clinical trial development for rare diseases. To increase enrolment of historically underrepresented populations, sponsors may strengthen community engagement by providing cultural competency training for clinical investigators and site staff to better engage with participants from different backgrounds, streamline informed consent where risks are low, provide patient leaflets in multiple languages, and provide language assistance for participants with limited English proficiency.[15]

Decentralised trials

Traditionally, clinical trials have been conducted at specific clinical trial sites. However, the burden this can have on participants is well-recognised, and regulatory guidance has been developed to facilitate the conduct of decentralised clinical trials.[16] Decentralising clinical trials will allow some or all trial-related activities to take place at trial participants' homes or other convenient locations instead of having them visit research sites, and include options such as an electronic informed consent.[17] Reducing barriers to participation may increase the diversity of participants with rare diseases, and improve accessibility and retention.

Conclusion

Population diversity in clinical trials is essential; however, it poses unique challenges for rare

diseases. The regulatory guidance encourages sponsors to do better, but many trials are not yet enrolling a diverse population that is reflective of the target population. By leveraging adaptive study designs, culturally tailoring patient engagement, and decentralising trial sites, sponsors can be equipped with strategies to increase population diversity in rare disease trials, which is both an ethical and scientific necessity. However, with recent cracks in regulatory legislation, there are concerns about the commitment from authorities, the obligation of sponsors, and the acknowledged importance of clinical trial diversity and health equity.

Acknowledgements

The author would like to thank Dr Heather L. Mason for supporting the development of this article and for content review and editorial assistance.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by her employer or EMWA.

Disclosures and conflicts of interest

The author is employed by BioMarin Pharmaceutical. The author declares no conflicts of interest.

References

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH E3 guidelines: Structure and content of clinical study reports. Available from: https://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
2. Clark LT, Watkins L, Piña IL, et al. Increasing diversity in clinical trials: overcoming critical barriers. Curr Probl Cardiol. 2019;44(5):148–72. doi:10.1016/j.cpcardiol.2018.11.002
3. Greenblatt DJ, Harmatz JS, Roth T. Zolpidem and gender: are women really at risk? J Clin Psychopharmacol. 2019;39(3):189–99. doi:10.1097/JCP.0000000000001026
4. European Commission. Clinical trial regulation (EU) No 536/2014 [cited 2025 Jan 02]. Available from: https://ec.europa.eu/health/human-use/clinical-trials_en
5. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH E5: Ethnic Factors in the Acceptability of Foreign Clinical Data. 1998 [cited 2025 Jan 02]. Available from: https://www.ich.org/page/efficacy-guidelines
6. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH E17: General Principles for Planning and Design of Multi-Regional Clinical Trials. 2017 [cited 2025 Jan 02]. Available from: https://www.ich.org/page/efficacy-guidelines
7. US FDA. FDA action plan to enhance the collection and availability of demographic subgroup data [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/89307/download
8. US FDA. Collection of race and ethnicity data in clinical trials: Guidance for industry and FDA staff. 2016 [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/75453/download
9. US FDA. Collection of race and ethnicity data in clinical trials: Guidance for industry and FDA staff. 2024 [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/175746/download
10. US FDA. Enhancing the diversity of clinical trial populations – eligibility criteria, enrollment practices, and trial designs: Guidance for industry. 2020 [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/127712/download
10. US FDA Diversity Action Plan [cited 2025 Jan 02]. Available from: Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies Guidance for Industry (Draft) 2024 [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/179593/download
11. EMA. Orphan designation: Overview [cited 2025 Jan 02]. https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview
12. US FDA. Rare diseases: Considerations for the development of drugs and biological products. Guidance or industry [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/119757/download
13. US FDA. Adaptive designs for clinical trials of drug and biologics. Guidance for industry [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/78495/download
14. Reopell L, Nolan TS, Gray DM II, et al. Community engagement and clinical trial diversity: navigating barriers and co-designing solutions – A report from the "Health Equity through Diversity" seminar series. PLoS One. 2023;18(2):e0281940. doi:10.1371/journal.pone.0281940
15. EMA. Facilitating decentralised clinical trials in the EU [cited 02 Jan 2025]. Available from: https://www.ema.europa.eu/en/news/facilitating-decentralised-clinical-trials-eu
16. US FDA. FDA takes additional steps to advance decentralised clinical trials [cited 02 Jan 2025]. Available from: https://www.fda.gov/news-events/ press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials#:~:text=Today%2C%20the%20U.S.%20Food%20and,than%20traditional%20clinical%20trial%20sites.

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