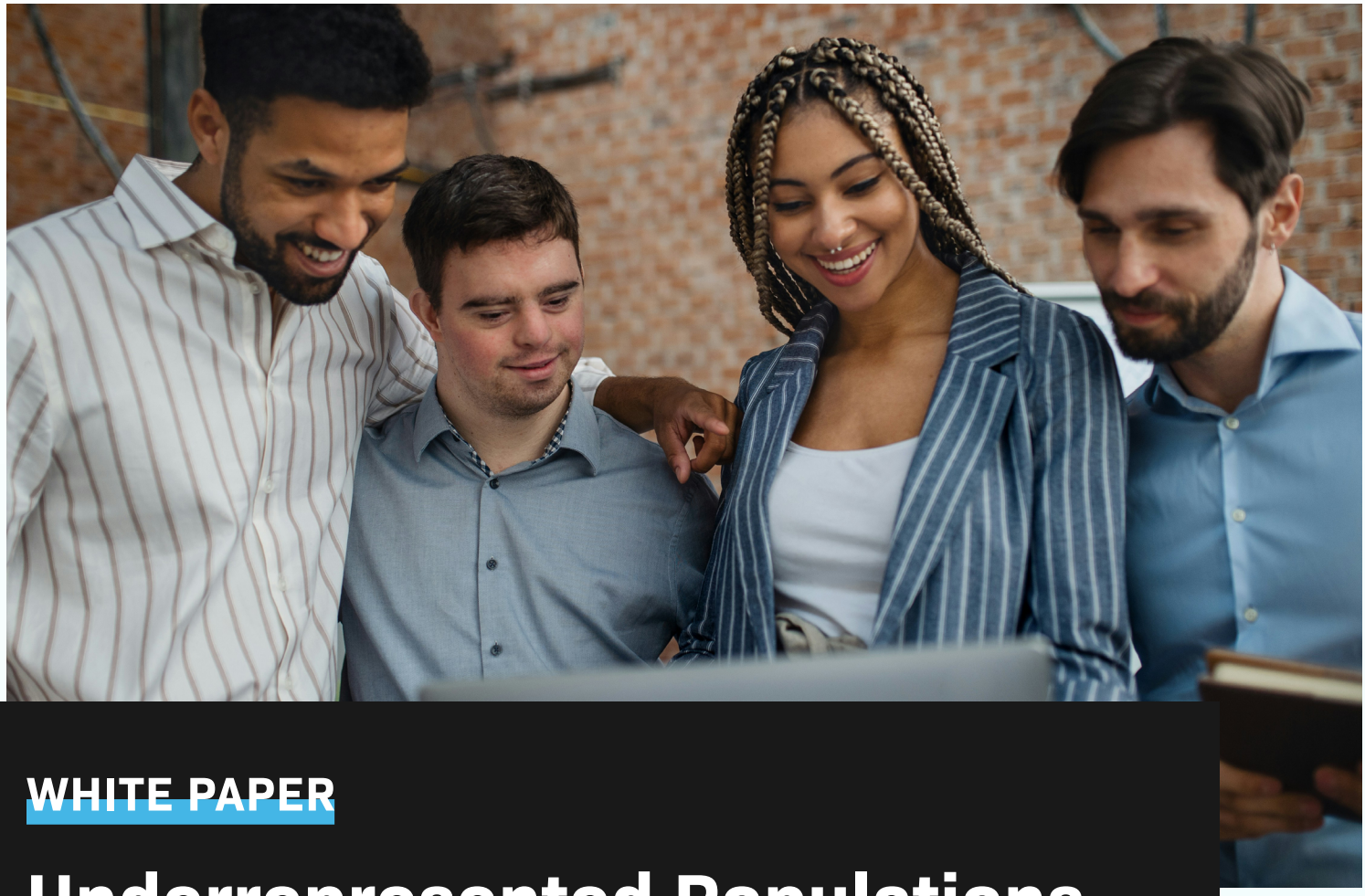

WHITE PAPER

Underrepresented Populations in Clinical Trials: Considerations, Diversity, Accessibility, and Patient Centricity

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INTRODUCTION

Lack of diversity and accessibility is an important concern in clinical research, where lack of equal representation or exclusion of specific population groups may threaten the validity and generalizability of research results. This means that the effectiveness of new drugs, therapies, or healthcare technologies may be less well understood in the wider population. In our white paper series, 'Enhancing Representation in Clinical Trial Populations,' we will be exploring underrepresentation of various populations within clinical trials, and will discuss some of the challenges, considerations, and potential strategies that might improve inclusion, accessibility, and more equitable representation in clinical research.

The terms 'special', 'diverse', and 'vulnerable' are often used in the context of clinical trials to describe these population groups.[1] Here, the term 'underrepresented' populations will be used, specifically referring to minors younger than eighteen years, geriatric populations, specific ethnic and racial populations, individuals in countries unlikely to gain access to drugs being investigated, individuals living in rural communities[1], as well as people with disabilities or impairments. Such populations have been historically, and are still, underrepresented in clinical research for several reasons, and increasing diversity in clinical trials is critical to ensure that all populations can benefit from clinical research and advancements in healthcare.

This white paper describes the current landscape of diversity and accessibility in clinical research, specifically the considerations for including underrepresented patient populations and regulatory guidance existing on the topic, providing the necessary context on which the series will build further.

CONSIDERATIONS FOR INCLUDING UNDERREPRESENTED POPULATIONS IN CLINICAL RESEARCH

Improving inclusion of underrepresented populations in clinical trials requires a nuanced approach, recognizing that each patient group presents distinct considerations and requirements.

Minors and the elderly

When infants and older adults participate in clinical research, specific risks are naturally involved. Age-related physiological features, e.g., differences in drug metabolism, organ toxicities, and adverse events, are all fundamental aspects to consider when designing such trials.[1] The likelihood of adverse drug reactions is higher in geriatric populations, as well as the presence of co-morbid conditions and polypharmacy.[1,2] Conducting trials in children is associated with additional ethical and feasibility considerations, as made clear by their protected status in IRB and regulatory guidance. It is also widely acknowledged that without sufficient study, off-label use of medication, or deprivation of medication advances, may put younger populations at greater risk.[3] In recognition of the need, the inclusion of children in medication trials for relevant conditions has been both incentivized and in some cases mandated by regulators.

Although it is accepted that study drugs should be assessed in those populations who will likely make use of the treatment, exclusions based on co-morbid conditions and concomitant medications (polypharmacy), as especially common in the elderly, may lead to inadequate representation of the intended patient group.[4] Clinical trial populations should be clinically relevant.[4]

Specific ethnic and racial groups

The ongoing challenge of marginalization of certain ethnic and racial groups persists in modern clinical research. This is likely influenced by an extraordinarily complex set of factors including history of socioeconomic discrimination, biases and differing cultural understandings of diagnosis and treatment, misinformation, and distrust of the research and medical industry as a whole. Researchers should bear in mind the historical context of racism and discrimination, the basis of bias, and the legacy of unethical research (such as the Tuskegee syphilis study), to have insight into the lack of trust in research and attitudes that may exist within specific populations.[1]

Genetic and disease predisposition variances exist in specific racial and ethnic groups.[1] To be able to investigate and improve our understanding of differences in treatment responses in specific patient groups (where genetic variances can be implicated), the inclusion of minority racial and ethnic groups is needed.[4] Data from such populations should be analyzed to aid in identifying population-specific signals.[4]

It's important to note that additional considerations may come into play when different racial or ethnic groups are included in clinical trials in those instances where healthcare technology and training were developed without data from those patient groups. For example, recent investigations of wearable devices for use in clinical research have unveiled the importance of evaluating potential measurement errors that may arise across different racial and ethnic groups. In one such investigation, it was revealed that inaccurate heart rate measurements from wearable devices employing photoplethysmography occurred up to 15% more in people with darker skin due to the greater levels of melanin absorbing more green light compared to white skin.[5] Similarly, certain reviews have indicated overestimation of blood oxygen saturation levels determined by pulse oximetry devices in skin of color again due to increased light absorption based on the melanin levels in darker skin.[6]

Moreover, in specific dermatology trials, it's crucial to account for diversity when training clinicians to apply dermatological rating scales as most training literature shows examples of dermatological disease only on white skin.[7] Dermatological symptoms can appear differently, and be difficult to discern on skin of color, which can often lead to misdiagnoses and inaccurate severity assessment. At Signant Health, our in-house medical experts developed a diverse set of training images for atopic dermatitis, that can increase the reliability of clinician-reported measures in such trials to overcome these existing diagnostic barriers.

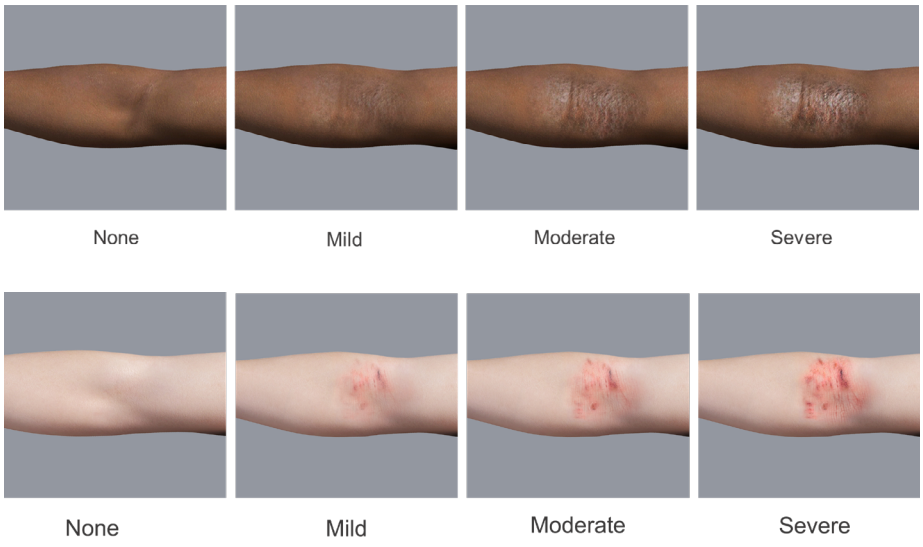

Figure 1. Example images for rater training scales for identification of lichenification in atopic dermatitis on skin of color (above) and excoriation on white skin (below).

Rural communities

Rural communities often experience significant health outcome disparities in comparison to urban communities, yet remain underrepresented in clinical research based on several factors, such as logistical difficulty, financial barriers, educational and cultural factors, as well as limited awareness of and access to clinical trials.[8] Therefore, it is very important to consider the significance of these factors within the context of this patient group, and attention should be paid to overcome these challenges, ensuring that trial participation becomes feasible and accessible to rural communities.

People with disabilities

People with disabilities tend to be impacted by more adverse health outcomes compared to their non-disabled counterparts, often experiencing a higher rate of chronic conditions and comorbidities.[9] Despite this, people with disabilities are largely excluded from clinical research, and even when people with disabilities are included in clinical trials, they are not provided with the adequate support or accommodations to assist their participation in the trial.[10]

Making efforts to improve accessibility for people with disabilities to participate in clinical trials remains vital to ensure that clinical trial results accurately reflect the intended patient population. To improve accessibility for people with disabilities in clinical trials, researchers must take into consideration the unique needs of the disability or specific impairment. Such considerations are important, to put in place the appropriate accommodations and assistive technologies needed to allow people with disabilities to fairly participate in the clinical trial.[11]

People in countries involved in clinical trials for which there is no possibility of later receiving the marketed drug

Many drugs approved by the US Food and Drug Administration (FDA) are often unavailable in the countries where the clinical research was initially conducted. Furthermore, some of these ex-US clinical trials occur in countries where even marketed drugs may be difficult to obtain due to income or national insurance regulations. This raises concerns about equitable access to new therapeutic developments. As a result, researchers must consider the ethical implications of conducting clinical studies in countries where patients will be unlikely to later benefit.[12]

INCREASING DIVERSITY: BROADENING ELIGIBILITY CRITERIA AND EXPANDING STUDY POPULATIONS

Failure to include relevant patient groups can result in inadequate or absent safety and efficacy information applicable to patients who might ultimately use the drug post-approval.[4] Increasing diversity in clinical trials is therefore crucial, to ensure the inclusion of clinically relevant patient populations.[4]

The US FDA guidance document on '*Enhancing the Diversity of Clinical Trial Populations*', places special emphasis on avoiding unnecessary exclusions and broadening eligibility criteria in trials, to ensure that enrolled patients represent those who will most likely, ultimately, use the drug.[4] As more safety data become available during a program, exclusions based on concomitant medication usage and the presence of comorbidities should reduce accordingly.[4] Furthermore, the guidance also mentions that "reasonable accommodations" may be needed to ensure participation and hence inclusion of specific patient groups.[4] In this way, the effects of demographic characteristics (such as race, ethnicity, and age) and non-demographic characteristics (such as the presence of comorbidities or disabilities), as well as the therapy's benefit-risk profile, can be adequately investigated.[4] The FDA also recently released a guidance document on developing Diversity Action Plans, to improve enrollment of underrepresented populations.[13]

INCREASING FOCUS ON PATIENT CENTRICITY

The FDA released a series of four methodological guidance documents, to support patient-focused drug development. These guidances provide recommendations and strategies for incorporating patient perspectives, enhancing diversity in clinical trial populations, and improving the efficiency and effectiveness of clinical trials, facilitating accessibility and relevance of new therapies to a wider population.

Key concepts of patient input, and methods of addressing representative data collection, are addressed in the first guidance document, to ensure that the perspectives and experiences of a diverse range of patients are considered in the drug development process.[14] Recommendations, such as having the enrollment criteria carefully designed to properly reflect the target population, having patients self-report their input, and tailoring methods of data collection according to the specific needs of the patient group, are outlined.

The first guidance document also emphasizes that if the study patient sample does not reflect the broad patient characteristics of the target population, that patient experience data are not necessarily generalizable to the wider population. To achieve sufficient representation, the guidance regards factors, such as socioeconomic and demographic backgrounds, cultural backgrounds and spoken language, literacy and health literacy, as well as clinical characteristics to be considered.

Socioeconomic and demographic background

- Include persons from all relevant demographics within the target population, including: age, sex, race/ethnicity, level of education, socioeconomic status to the extent possible

Cultural background and spoken language(s)

- Include persons from all relevant cultures and languages within the target population to the extent possible
- Ensure that results from the research study apply to the entire target population. People from different cultures may describe their signs and symptoms of a disease or condition differently and/or may have different values and preferences

Literacy and health literacy

- Include persons with all levels of reading, writing, problem solving abilities to the extent possible. Also consider a person's speaking ability

Clinical characteristics

- Range of severity of disease or condition
- Range of symptoms and/or functional impacts experienced (especially for those diseases or conditions with symptom heterogeneity, such as migraines and some rare diseases)
- Range of comorbidities
- Range of physical and cognitive abilities

Figure 2. Factors to consider to achieve sufficient representation, as presented in the FDA guidance "Patient-Focused Drug Development: Collecting Comprehensive and Representative Input".

Expanding upon this in the second guidance document, information on methods to obtain patient input are provided, where methods to overcome barriers to obtaining self-reported patient data are a focal point.[15] This ties in with the theme of inclusion, aiming to ensure that all populations are being considered. The guidance underscores the importance of recognizing the different capabilities of patients, such as differences in physical, sensory, intellectual, and communication abilities, as well as some approaches to ensure accessibility and usability.[15] Importantly, the guidance stresses that when planning research, the study sample should be representative and reflect the relevant population of interest, accounting for the full spectrum of the disease and diversity among patients.

The third guidance document outlines steps to select and develop a fit-for-purpose clinical outcome assessment (COA), where accessibility features are also taken into account.[16] In this guidance document, emphasis is placed on universal design, referring to the principle of designing research studies in a manner that maximizes inclusion and accessibility for all patients, regardless of factors such as age, gender, race, ethnicity, disability, or socioeconomic status.

The last draft guidance in the series emphasizes that the aim of COAs is to "reflect, directly or indirectly, how patients feel, function or survive." It lays out methods, standards, and technologies to aid in the interpretation of COA-based results as well as to evaluate what is considered a clinically meaningful change in the context of patient experience for the regulatory decision-making process.[17]

While the FDA's guidances on patient-focused drug development stresses the importance of improving diversity and accessibility in clinical trials, there is more work to be done to practically address the underlying barriers and disparities that exist. Continued efforts to engage with these populations, address cultural and logistical barriers, build trust, and promote diversity in research leadership are essential.

CONCLUSION

Clinical research is fundamental to the advancement of health care for all. Yet studies suggest that many clinical trials fail to ensure the inclusion of groups the studies might ultimately help. Consequently, researchers may enroll populations that are not fully representative of the target population, leading to compromised generalizability of the clinical trial results.

Limiting the participation of underrepresented populations in clinical trials raises concerns surrounding the validity of the trial's outcomes and may lead to uncertainty around the therapy's safety and efficacy within the excluded population.[18] Excluded populations may already face health disparities due to various factors, such as socioeconomic, cultural, environmental, race or ethnicity, age, or disability status. Without representation, these pre-existing health disparities may be exacerbated, contributing to significant economic loss due to shorter life expectancy and overall poorer health in these populations.[19]

Furthermore, exclusion of these populations in clinical trials may lead to larger repercussions within the industry as a whole. By failing to account for diversity in clinical trials, variation is reduced and may hinder the discovery of new and effective therapies across the wider population. It can also potentially lead to inadequate accrual, which remains a leading cause of early termination of clinical trials and trial failure.[20] In addition, poor representation of these populations in clinical trials may perpetuate systemic biases and contribute to further marginalization of these groups, and deepen the mistrust of the healthcare system and clinical research industry.

Addressing diversity and inclusion in clinical trials is therefore necessary to establish equitable access to healthcare and to improve health outcomes for all populations.

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