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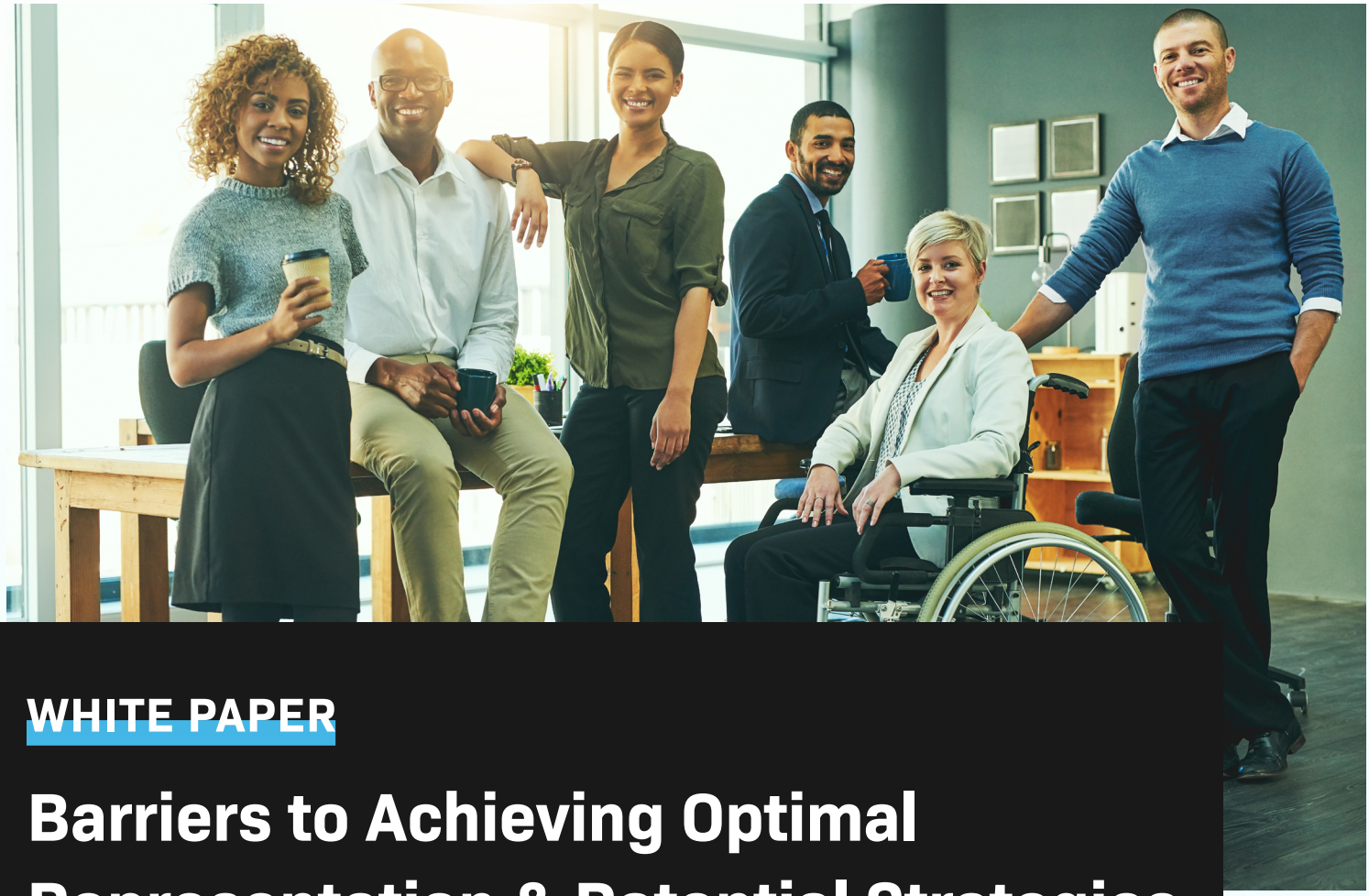

WHITE PAPER

Barriers to Achieving Optimal Representation & Potential Strategies to Enhance Inclusion in Clinical Trials

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INTRODUCTION

The previous white paper in our series, 'Enhancing Representation in Clinical Trial Populations', highlighted the critical importance of diversity and patient centricity in clinical trials. The absence of diversity and accessibility in clinical research poses a critical issue, as the underrepresentation or exclusion of certain population groups can compromise both the validity and generalizability of study outcomes.[1] In addition, this gap can lead to development of treatments that are efficacious but may not be effective with certain subpopulations, perpetuating health disparities.[2] Thereby, continued focus on inclusion, patient centricity, and addressing barriers to participation is essential to achieve equitable healthcare outcomes. Importantly, achieving diversity in clinical trials is crucial not only for scientific rigor but also for meeting regulatory standards.

In this second white paper, we will review different barriers to achieving diversity in clinical trials, and explore some potential strategies to overcome such challenges, while presenting some case examples. We will also explore the role of clinical trial technologies and how these may help to support diverse and equitable clinical trials and patient centricity.

BARRIERS TO ACHIEVING DIVERSE PARTICIPATION IN CLINICAL TRIALS

Several barriers prevent diverse participation in trials, particularly amongst marginalized groups. These barriers span systemic, logistical, and sociocultural dimensions, often intersecting in ways that perpetuate underrepresentation in clinical research. This section outlines the key obstacles to diversity in clinical trials.

Mistrust in Medical Institutions

Mistrust in medical and research institutions remains a significant barrier to clinical trial participation among underrepresented groups. While this mistrust is often rooted in historical injustices (e.g., the Tuskegee Syphilis Study), it is not solely confined to the past. Present-day disparities in healthcare outcomes, such as the disproportionately higher mortality rates experienced by Black and Latinx populations during the COVID-19 pandemic, have deepened these concerns. Many individuals from marginalized communities view clinical trials as an extension of a healthcare system that has historically failed to prioritize their well-being.

Logistical and Socioeconomic Barriers

Logistic and socioeconomic factors present additional challenges for achieving diversity in clinical trials. Participating in a trial often requires significant time and resources, such as transportation to trial sites, time away from work, and funds to cover incidental costs like parking and childcare. These barriers disproportionately affect low-income populations, which are more likely to include racial and ethnic minorities.[3] Although clinical trials generally offer reimbursements, at least in the United States (US), taking time away from work or spending extended hours away from home responsibilities may still be untenable for many individuals with limited resources. Leveraging decentralized elements in clinical trial design offers a promising solution to these logistical barriers, an approach we will explore further in the following white paper in this series.

Additionally, language barriers pose significant challenges. In the US, patients with limited English proficiency (LEP) are often excluded from clinical trials because researchers fail to provide adequate translation services or culturally appropriate materials. Providing interpreters and ensuring that informed consent forms (ICFs) and study materials are translated into multiple languages is essential for overcoming this barrier.

Systemic Barriers

There are systemic barriers to achieving diversity in clinical trial participation. One of the primary systemic barriers is geographic access. Trials are frequently concentrated in large academic medical centers, often located in urban areas, limiting participation opportunities for patients in rural regions. This limitation is especially concerning, as rural residents often face substantial health disparities due to restricted access to specialized medical care and emergency services compared to urban populations. Furthermore, rural communities generally have lower income and education levels[4], with education being a key predictor of interest in clinical trial participation.

Institutional resources are another critical determinant of trial availability. Many underfunded hospitals and clinics, which are often in less-affluent areas, lack the infrastructure needed to conduct clinical trials. Hospitals in low-resource settings also frequently lack the administrative capacity to navigate the complex regulatory requirements associated with clinical research, effectively excluding these sites from participation. This exclusion fosters a cycle of underrepresentation that is difficult to break without addressing systemic inequities. Consequently, individuals in disadvantaged areas are often left out of clinical trials. Sociodemographic disparities between affluent and lower-income areas can lead to a disproportionate impact on trial accessibility for communities of color, including Black, Indigenous, and People of Color (BIPOC) populations, further limiting their access to potentially beneficial clinical research.[5]

Inadequate Awareness and Outreach

Lack of awareness about clinical trials is another significant barrier to participation for marginalized groups. Outreach efforts have historically been insufficient or poorly targeted. Traditional recruitment methods, such as referrals through large healthcare systems, often fail to reach marginalized communities that may not have access to these networks. In many cases, the issue is not that these populations are unwilling to participate, but rather that they are not being approached. This systemic exclusion not only reduces the diversity of clinical trial participants but also perpetuates existing health disparities.

Cultural Competence and Bias Among Researchers

A lack of cultural competence among researchers can be a significant barrier to achieving diversity in clinical trials. Healthcare providers lacking the necessary cultural sensitivity to effectively engage with underrepresented communities can negatively impact enrollment of potential participants from diverse backgrounds.[6] Addressing this issue requires targeted training in cultural competence for clinical research teams, as well as greater diversity within the research workforce itself. Institutions that struggle to recruit and retain diverse staff are likely to encounter similar challenges when trying to enroll diverse participants in clinical trials. Ensuring that research teams reflect the diversity of the communities they serve can help build trust and improve communication with potential trial participants.

Healthcare providers' biases can also affect whom they refer to trials. Some healthcare providers may not offer trial participation to patients from underrepresented groups due to their own biases or assumptions about patients' willingness or ability to comply with trial protocols.[7] These factors collectively result in fewer opportunities for these populations to engage in clinical research.

Balancing Recruitment Efforts

Achieving diversity in clinical trials is vital, yet we must carefully balance recruitment efforts, especially in settings where healthcare access is limited. For low-income populations, particularly in countries without universal healthcare such as the US, clinical trials may appear as a rare opportunity for "better care." However, this can lead to ethical issues, especially in Phase I trials, where participants face significant risk without therapeutic benefit.

In early-phase studies, low-income individuals are often drawn by financial incentives. While compensation is appropriate, it raises concerns about whether participants are fully informed of the risks, or if economic need drives them to overlook them. To address this, protocols must emphasize fairness and transparency. ICFs should clearly present risks without hinting at healthcare benefits that don't exist. Audio recording of consent discussions may be a vehicle to enhance oversight, ensuring participants fully understand the trial's nature and risks.

POTENTIAL STRATEGIES TO OVERCOME RECRUITMENT, ENROLLMENT, AND RETENTION/ENGAGEMENT CHALLENGES

Participant recruitment, enrollment, and retention/engagement challenges are often associated with minority/underrepresented groups in clinical research.[8] Special attention to and awareness of these barriers, and strategies to overcome those, are needed. Here, we outline some strategies that can aid in overcoming these challenges.

Study teams should understand the specific cultural, socio-economic, and demographic landscapes of the target audience, in order to set up effective recruitment campaigns.[9] Robust recruitment tactics should be utilized, including determining the most suitable communication channels for the specific population, developing targeted and culturally-sensitive recruitment materials, and using appropriate language.[9,10] Importantly, caregivers are often the target audience where underrepresented populations are recruited, which should be taken into account when setting up recruitment strategies.[9] In addition, studies requiring caregiver support for the duration of the study, such as dementia studies, or pediatric studies, pose even more recruitment challenges that should be considered.[11]

Caregivers of individuals with dementia or children with special needs are often overburdened by their caregiving responsibilities, leaving them with limited time and energy to participate in research studies. This issue is further compounded by the complexity of their loved ones' care, which demands constant attention and support. In some cultures, caregiving is expected to be provided by family members rather than paid professionals. Additionally, underrepresented populations may face financial barriers that prevent them from accessing formal care services. Recruiting caregivers for research is challenging not only due to their time constraints but also because of their hesitancy to engage in studies that could impose further emotional and logistical burdens. To address these challenges, adaptive recruitment strategies such as utilizing electronic health records (EHRs) to identify eligible participants, personalized outreach from healthcare providers, and flexible communication options such as remote consenting and assessments can help accommodate caregivers' schedules. These tailored approaches recognize the unique burdens caregivers face while enabling their participation in essential research.[12]

As described in our first white paper, researchers should understand the historical experience of specific racial and ethnic communities with clinical research. Targeted and tailored approaches can then be utilized to optimize the recruitment and consenting processes, and to ensure participant retention, engagement, and compliance with trial procedures. Furthermore, sponsors should collaborate with relevant stakeholders and community organizations, which can contribute to overcoming such barriers.[10] Another important aspect to consider is the demographic distribution of the trial population[9], e.g., countries included and the corresponding participant numbers. Study teams should bear in mind the population breakdown when thinking about recruitment tactics.[9]

While the US Food and Drug Administration (FDA) draft guidance on Diversity Action Plans was withdrawn from their public website under the new governmental administration in January 2025, the principles remain important. This draft guidance detailed proposed requirements for sponsors to submit Diversity Action Plans for Phase III trials (or other pivotal studies).[13] The implementation of identified actions to increase diversity will help improve the generalizability of trial results across the intended target population. The draft guidance indicated that these plans should describe the enrollment and retention strategies for the study population and include specific study enrollment goals per demographic characteristic (including race, ethnicity, sex, and age group). Sponsors were also encouraged to consider other relevant factors when setting up these goals, such as geographic location, gender identity, sexual orientation, socioeconomic status, physical and mental disabilities, pregnancy and lactation status, and co-morbidities. Community engagement, providing cultural competency training for site staff, and improving participants' understanding of the research were some suggested approaches that the FDA outlined.

Sickle cell disease (SCD) studies may serve as a case example where many of the considerations and strategies discussed are applicable. The prevalence of SCD, an autosomal-recessive genetic disorder, is higher in specific ethnic and demographic groups, with a high prevalence among descendants of sub-Saharan Africa.[14,15,16] The prevalence of SCD thus varies by country. In SCD trials including countries with lower SCD prevalence, a special focus on engagement of patients is needed to ensure participant recruitment and retention, as well as compliance with study activities.[17,18] One strategy is to ensure input from patient groups and other relevant stakeholders to tailor approaches, thereby addressing and overcoming barriers known to exist in SCD trials.[18] Generally, patients' understanding of the research can impact their recruitment and retention in clinical studies. It is important to provide appropriate, patient-friendly educational content.[9,10] Such content may include details around what clinical research entails, the specific disease, and the study itself.

ENHANCING INCLUSION OF UNDERREPRESENTED POPULATIONS IN CLINICAL TRIALS THROUGH ELECTRONIC INFORMED CONSENT (eCONSENT)

A critical aspect of clinical trials that may be impacted by the barriers we have discussed is the informed consent process which, if not tailored to the needs of underrepresented populations, can hinder participation of these populations in clinical trials.

Obtaining informed consent is one of the most important ethical components of clinical research, ensuring adequate information about the clinical trial, including treatment options, study activities, risks and benefits of participation, as well as data privacy and protection, is disclosed to the participant, allowing them or their legally authorized representative (LAR) to make an informed decision to voluntarily participate.[19] Traditionally, paper-based ICFs have been used to carry out the consenting process. However, these paper-based methods are associated with various issues that can compromise the effectiveness, efficiency, and inclusivity of the consenting process.[20]

Consequently, eConsent is becoming of increasing interest to supplement or replace paper-based informed consent processes and offers several advantages that can help improve the inclusion of underrepresented populations in clinical trials. It is important to note that, while eConsent platforms may facilitate an enhanced and accessible consenting process as will be outlined below, electronic processes should be supplemented with opportunities for direct in-person communication to mitigate misunderstandings and foster trust by ensuring sufficient comprehension of study participation by addressing queries face-to-face.

REMOTE CONSENTING

Typically, paper-based informed consent processes require participants to travel to the study site. Research shows that clinical trial sites are primarily located in urban areas with a greater density of medical centers and academic institutions which serve as clinical trial sites.[21] This may be challenging for individuals living in rural or underserved areas, and, as a result, these communities are commonly excluded from trial participation.

By deploying ICFs via an electronic system, eConsent platforms can be accessed remotely, removing the logistical and financial barriers associated with traveling to study sites. The remote flexibility of eConsent can not only allow individuals from diverse geographic locations to participate in clinical trials, but can also accommodate the varying needs and circumstances of participants, such as those with physical limitations, chronic disease, or caregiving responsibilities.[22,23] However, researchers should be aware of the potential limitations of employing eConsent remotely in these populations, including lack of access to suitable electronic devices, unstable or limited network coverage, and technological illiteracy.[24] Strategies to overcome these challenges will be expanded on further in our third white paper.

OVERCOMING LANGUAGE BARRIERS AND IMPROVING COMPREHENSION

Lack of availability of translated consent forms or overly lengthy consent forms containing complex medical jargon without the ability to readily tailor the language to the participant's needs can lead to poor comprehension of key study details, compromising the integrity of the consenting process or reluctance to participate in the study entirely.[25,26]

As a result, those with LEP or non-English speakers, as well as those with limited literacy levels may be unfairly excluded from clinical trials due to inefficient consenting procedures or may be excluded based on these criteria entirely.[27] Moreover, low literacy is more common in certain groups, such as the elderly, those with limited education, those with chronic conditions, individuals from low-income backgrounds, and minority racial and ethnic groups, compounding underrepresentation of these groups from clinical trials.[28]

Similarly to paper-based ICFs, eConsent platforms can offer ICFs in multiple languages, ensuring that non-English speakers or those with LEP can fully understand the trial. It can also be customized with simplified language, avoiding medical jargon and using plain language that is easier to comprehend. However, in contrast to paper ICFs where physical copies in different languages must be printed, distributed, and managed, eConsent platforms can dynamically offer language selection and tailored consent without logistical delay.

Additionally, eConsent platforms can incorporate videos and other interactive elements to present the trial information in a more engaging and accessible way and can aid in overcoming literacy challenges. This approach helps to ensure that linguistic and health literacy barriers are addressed, improving inclusion of these individuals in clinical trials. Furthermore, utilizing quiz elements to test understanding, the ability to identify time spent in certain parts of the ICF to review areas that may not have been read or understood, and the ability for the reader to flag content to ask questions about are all features that can help to ensure understanding of the content.

ADDRESSING CULTURAL SENSITIVITY AND CONCERNS AROUND DATA PRIVACY

ICFs are often developed without consideration of an individual participant's beliefs or cultural values, which may exacerbate existing mistrust of the clinical research industry within historically marginalized communities or make these minority groups less willing to participate.[29] In Western culture, a strong emphasis is placed on the rights of the individual to make decisions about their own bodies and health. Conversely, in some African and Asian cultures, the decision to participate is seen as a collective process, involving the community or family members.[30]

Consequently, researchers should consider these cultural nuances when designing consent processes, such as engaging with community leaders to ensure that ICFs are understandable for potential participants, or integrating informational sessions for families.[31,32] Importantly however, researchers should ensure that these accommodations do not interfere with the individual's voluntary decision to participate.

UTILIZING ARTIFICIAL INTELLIGENCE (AI) IN eCONSENT TO DRIVE GREATER DIVERSITY IN CLINICAL TRIALS

AI technologies are being increasingly implemented to trial processes to improve the probability of trial success, efficiency, generalizability, and patient centricity.[33] As such, there are a number of emerging opportunities to leverage AI in the informed consent process to improve the inclusion of underrepresented populations in clinical trials.

For example, AI algorithms can be trained to identify and eliminate biased language in consent forms that may unintentionally exclude or misrepresent certain groups, or can rephrase complex medical jargon, ensuring that participants with varying levels of health literacy can easily comprehend the content.[34,35]

In addition, AI-powered chatbots or virtual assistants can be implemented to provide support for participants through the consenting process. These tools can improve participant engagement by providing real-time feedback and clarification, as well as personalize the consent form based on participant experiences and preferences.[36,37]

While there is the potential for AI to enhance the informed consent process and address barriers to inclusion of underrepresented groups in clinical trials, more investigation into the risks related to data privacy, algorithmic bias, and regulatory requirements is needed before being routinely implemented in practice.

LEVERAGING SIGNANT HEALTH'S eCONSENT AND PATIENT ENGAGEMENT SOLUTIONS TO ENABLE BROADER PARTICIPATION AND OPTIMIZE RETENTION IN CLINICAL TRIALS

Signant Health's eConsent solution, Signant SmartSignals® eConsent, provides a range of feature options to facilitate comprehension and compliance, and accommodate the diverse needs of participants. SmartSignals® eConsent offers multi-lingual capability, remote access, self-service, as well as 24/7 user support. The solution also allows patients to step away while working through the ICF, which provides them the opportunity to reflect on the content and follow-up on specific aspects as needed. Furthermore, ICFs can be updated and deployed on a site-by-site basis, allowing for a simple reconsenting process, which includes relevant tracking. In addition, SmartSignals® eConsent offers an interactive consent experience, where multimedia can be incorporated to help create an engaging experience for patients and help improve their comprehension of the trial. Embedded video and audio playback, comprehension tests, and the ability to flag parts of the ICF to ask questions about during discussions with the investigator are all features that Signant SmartSignals® eConsent support. Patient engagement starts at the consenting process, where the trial participant's experience sets the foundation for the remainder of the trial. This is of particular importance for patient populations where distrust in research may exist.

Patient engagement and retention rates throughout a study can be optimized with Signant's patient engagement solution, available on bring your own device (BYOD) or a provisioned device alongside electronic clinical outcome assessments (eCOAs) - uncomplicating patient experience with a single platform/app. This feature can include information on the indication and provide detailed visit information, thereby ensuring that patients are equipped throughout the entire trial. Importantly, engagement strategies should be tailored per study, with information included to be configured in order to suit the particular needs of an indication/protocol.

CONCLUSION

Ensuring diversity in clinical trials is not just a scientific imperative but a crucial step toward achieving equitable healthcare outcomes. The underrepresentation of certain populations in research not only limits the generalizability of study findings but also perpetuates health disparities, leading to treatments that may not be equally effective for marginalized groups. Overcoming the systemic, logistical, and cultural barriers to equitable participation requires a coordinated effort from all stakeholders in the clinical research field.

By building trust, raising awareness, and addressing logistical and socioeconomic challenges, researchers and sponsors can begin to dismantle the obstacles that prevent underrepresented communities from participating. Signant Health's innovative tools, such as eConsent and patient engagement solutions, offer practical strategies for making clinical research more inclusive, accessible, and patient-centric. These tools, along with culturally sensitive outreach and flexible trial designs, can help bridge the gap between researchers and diverse patient populations.

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