Advancing the Landscape: Increasing Diversity in Clinical Trials

EXECUTIVE SUMMARY

The lack of diversity that has plagued clinical research continues to negatively impact the scientific evidence base of medical product safety and efficacy. Despite initiatives designed to create more stable clinical trial populations, issues still exist at the study, site, and sponsor level, and system-level change remains elusive. As such, the Clinical Trials Transformation Initiative (CTTI) considered whether it should begin a project to address this issue.

CTTI's literature scan (see appendix) and corresponding exploratory conversations with experts and key stakeholders revealed that a comprehensive, collaborative strategy is critical to overcome the barriers to clinical trial diversity that affect patients, providers, investigators, and sponsors. The findings from that landscape assessment and working group conversations are detailed below, and have since been used to create a new CTTI project on Increasing Diversity in Clinical Trials, which is currently underway.

Methods

To thoroughly understand the complex issues underpinnning the lack of diversity in clinical trial populations, CTTI organized a multistakeholder working group comprising 21 representatives. The group conducted a landscape assessment to identify:

1. The scientific rationale for increasing diversity in clinical trials
2. The factors that contribute to and limit the success of existing initiatives to increase diversity in clinical research

CTTI also conducted interviews with 10 experts and key stakeholders from academic institutions, industry, healthcare systems, and the non-profit sector to confirm or identify additional factors that contribute to or limit the effectiveness of existing initiatives designed to alleviate the diversity issue. Collectively, the interviewees had experience successfully mobilizing initiatives to recruit and retain a broad range of patient populations, including Native Americans, African Americans, Latinos, and Asian Americans who reside in urban and rural communities.

Findings

1. Scientific Rationale for Increasing Diversity in Clinical Trials

Several differences in gender, race, and ethnicity driven by genetic, physiological, and environmental factors lead to inter-individual variances in the pharmacokinetics (PK) and pharmacodynamics (PD), efficacy, and safety of drugs.[1]

- In women, these factors include, but are not limited to, sex hormones; changes in sex hormones due to menstruation, pregnancy, menopause, oral contraceptives; body fat composition; and environmental factors related to disparities in the practice of medicine between men and women.[2-5]

- In racial and ethnic minorities, disparities result from an interplay of *intrinsic* individual characteristics, such as the route of drug administration, and *extrinsic* factors such as culture, diet, the practice of medicine, and socioeconomic status.[6-10] One example illustrating this issue is the African American atrial fibrillation (AF) "double paradox," which demonstrates how racial disparities in the practice of medicine impact overall population-level disease outcomes.[11]

Current accrual patterns in U.S. clinical trials are insufficient to drive the collection and analysis of robust safety and efficacy for underrepresented, uniquely vulnerable populations. While advances in genomic research hold great promise for developing targeted therapies for diverse populations, these efforts will need to be grounded in an understanding of environmental factors that drive complex epigenetic dynamics.

Barriers to Increasing Diversity in Clinical Trials

All clinical trial stakeholders, including patients, providers, investigators, and sponsors, contribute to the barriers and strategies to increase engagement of diverse patient populations in clinical trials..

- **Patients**

  Patient-level barriers, which differ across racial and ethnic minority communities, include mistrust of clinical research; investigational medical product safety concerns; logistical barriers related to transportation, work, and family caretaking responsibilities; insurance status; health literacy; lack of awareness of clinical trials; English conversational fluency and literacy; and immigration status.[12-18]

- **Providers**

  Providers play a critical gatekeeping role for underrepresented populations in clinical trials. Provider-level barriers that limit the effectiveness of clinical trial research education and referrals include distrust of clinical research among minority and minority-serving providers; concerns related to patient time and financial burden; concerns related to patient co-morbid conditions and the safety of investigational medical products; ineffective communication with patients about clinical trial research opportunities; poor communication between specialists and primary care physicians; and competing time pressures inpatient visits.[14,18-24]

- **Investigators**

  Barriers related to investigators and research teams include lack of cultural competency, pre-existing partnerships with community partners in diverse communities, and lack of resources and staffing to develop and implement accrual strategies that are responsive to the barriers experienced by underrepresented populations. Common strategies used to address investigator-level barriers include cultural competency training and intentional hiring practices that diversify research teams.

- **Sponsors**

  Sponsors can play a critical role in aligning resources, incentives, and accountability mechanisms to accrue underrepresented populations. Individual sponsors have undertaken a variety of strategies to increase diversity in clinical trials, including specialized training programs for new minority investigators, intentional partnerships with sites that have proven success in the accrual of underrepresented populations, and partnerships with community-based organizations.

Promising Practices: Multistakeholder Strategies for Success

A multi-faceted approach that takes into account the barriers associated with the participation of diverse populations in clinical trials is key to designing a successful strategy to foster clinical trial diversity.

- One example of this type of multistakeholder strategy was the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study.[25] Because Native Americans have the highest prevalence of type 2 diabetes of any racial or ethnic group, the University of Oklahoma included representative organizations from this key demographic and integrated the study into the health care ecosystem. The result was a study that successfully engaged and retained Native American adolescents.

- The University of Alabama at Birmingham's Comprehensive Cancer Center patient navigator program sought to increase the participation of African Americans in clinical trials by providing community education and conducting needs assessments to support patients. The result was a significant increase in African American enrollment and retention in clinical trials.[26]

Factors that Contribute to or Limit the Success of Existing Diversity Initiatives

CTTI conducted interviews with 10 experts and key stakeholders recruited from academic institutions, industry, healthcare systems, and the non-profit sector to identify factors contributing to or limiting initiatives to increase clinical trial diversity. An analysis of the interview data revealed four key factors:

- Consideration of the whole protocol medical product development program: This included an expansion from the typical focus on recruitment and retention, including an examination of overly narrow inclusion and exclusion criteria that can disproportionately impact underrepresented populations, and innovative data sources and design strategies to develop actionable data.

- Coordinated action across key system-level actors: Multifactorial barriers require multilevel, multistakeholder strategies with buy-in and commitment from leadership .

- Limited efforts to scale and replicate: Study-level strategies are insufficient to develop long-term success. Instead, efforts are needed to develop a scalable clinical trial infrastructure that is responsive to the needs of multiple stakeholders.

- Insufficient resource allocation: Strategies that prove value and impact will increase resources. Key decision-makers need to be kept abreast of progress and receive updates at key intervals to maintain leadership buy-in.

Conclusion

The lack of diversity in clinical research disproportionately affects ethnic minorities by producing gaps in knowledge about the risks and benefits of investigational medical products. CTTI's landscape assessment and exploratory interviews revealed that a systemic and comprehensive strategy that includes multistakeholders is needed to overcome barriers to clinical trial diversity. The findings from this research informed a new project, Increasing Diversity in Clinical Trials, which is currently underway

Appendix: Resources Used in CTTI's Literature Review

1. U.S. Food and Drug Administration CfDEaR. Guidance Documents: International Conference on Harmonisation document E5, Ethnic Factors in the Acceptability of Foreign Clinical Data. 1998.
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