Published in final edited form as:

Contemp Clin Trials. 2022 May ; 116: 106740. doi:10.1016/j.cct.2022.106740.

Inclusion and Diversity in Clinical Trials: Actionable Steps to Drive Lasting Change

Michelle D. Kelsey, MD[a,b], **Bray Patrick-Lake, MFS**[c], **Raolat Abdulai, MD**[d], **Uli C. Broedl, MD**[e], **Adam Brown Sr, BA**[f], **Elizabeth Cohn, RN, PhD**[g], **Lesley H. Curtis, PhD**[b,h], **Chris Komelasky, MBA**[i], **Michael Mbagwu, MD**[j], **George A. Mensah, MD**[k], **Robert J. Mentz, MD**[a,b], **Amesika Nyaku, MD**[l], **Stephanie O. Omokaro, MD**[m], **Judy Sewards, BA**[n], **Kendal Whitlock, MPH**[e], **Xinzhi Zhang, MD, PhD**[o], **Gerald S. Bloomfield, MD, MPH**[a,b]

[a]Division of Cardiology, Department of Medicine, Duke University, Durham, NC, USA;

[b]Duke Clinical Research Institute, Durham, NC, USA;

[c]Evidation Health, Inc., San Mateo, California, USA;

[d]Sanofi, Cambridge, MA, USA;

[e]Boehringer Ingelheim GmbH & Co KG, Germany;

[f]ClinArk, Dayton, OH, USA;

[g]Hunter College, City University of New York, NY, USA;

[h]Department of Population Health Sciences, Duke University School of Medicine, Durham, NC, USA;

[i]SiteBridge, Chapel Hill, NC, USA;

[j]Verana Health, San Francisco, CA, USA;

[k]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA;

[l]Division of Infectious Diseases, Department of Medicine, Rutgers-New Jersey Medical School, Newark, NJ, USA;

[m]United States Food and Drug Administration, MD, USA;

[n]Pfizer Inc, New York, NY, USA;

Address for correspondence: Gerald Bloomfield, MD, MPH, 300 West Morgan Street, Durham, NC 27701. Phone (919) 668-8702. gerald.bloomfield@duke.edu.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

[o]National Institute on Minority Health and Health Disparities, National Institutes of Health, Bethesda, MD

Abstract

Background: Improving diversity in clinical trials is essential in order to produce generalizable results. Although the importance of representation has become increasingly recognized, identifying strategies to approach this work remains elusive. This article reviews the proceedings of a multi-stakeholder conference about the current state of diversity in clinical trials and outlines actionable steps for improvement.

Methods: Conference attendees included representatives from the United States Food and Drug Administration (FDA), National Institutes of Health (NIH), practicing clinical investigators, pharmaceutical and device companies, community-based organizations, data analytics companies, and patient advocacy groups. At this virtual event, attendees were asked to consider key questions around best practices for engagement of underrepresented populations.

Results: Community engagement is an integral part of recruitment and retention of underrepresented groups. Decentralization of sites and use of digital tools can enhance the accessibility of clinical research. Finally, improving representation among investigators and clinical research staff may translate to diverse clinical trial participants.

Conclusion: Improving diversity in clinical trials is an ethical and scientific imperative, which requires a multifaceted approach.

Keywords

diversity; inclusion; underrepresented populations; clinical trials

INTRODUCTION

Improving diversity in clinical trials is of the utmost importance, not only to enhance representation, but also to ensure the generalizability of, and trust in, results. Although much work has been done in this area, we have not yet realized the potential gains of initiatives to enhance diversity and inclusivity in clinical trials in the United States (U.S.). Among 32,000 individuals who participated in new drug trials in the U.S. in 2020, only 8% were Black, 6% Asian, 11% Hispanic, and 30% were age 65 and older, showing relative underrepresentation of these important demographic groups [1]. These estimates have worsened since 2019 [2] and are not aligned with U.S. Census data, which found 14.2% of the population was Black, 7.2% Asian, and 18.7% Hispanic. In contrast to these low trial participation statistics, underrepresented racial and ethnic minority groups carry a disproportionately high burden of chronic diseases that garner the most investment in drug research and development [3]. It is these groups of individuals who may benefit directly from inclusion in clinical research, to develop and refine effective treatments, thereby achieving improved overall population health. In this review, we report the proceedings of a two-day, multi-stakeholder conference focused on the state of diversity and inclusivity in clinical trials and outlined actionable steps for change.

METHODS

Conference attendees included key stakeholders in improving diversity across the clinical trial continuum, with representatives from the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), practicing clinical investigators, pharmaceutical and device companies, community-based organizations, data analytics companies, and patient advocacy groups (Supplementary Table 1). This think tank was organized and sponsored by the Duke Clinical Research Institute (DCRI) [4]. The event took place on April 28–29, 2021 and was held virtually due to the coronavirus 2019 (COVID-19) pandemic. Attendees were selected by Think Tank faculty and staff of the DCRI. Representatives from each organization also had an opportunity to invite others whom they thought may have important input. Attendees were asked to consider the following key, mutually agreed-upon questions: (1) What are the best practices for participant engagement with underrepresented populations during study design, recruitment, and trial execution? (2) How can we create mutual benefit and value that drives sustained engagement and retention of underrepresented populations? (3) How can the use of digital approaches increase diversity and retention, and how can we ensure that we use technologies to eliminate, rather than increase, disparities? (4) What are the characteristics and strategies of sites and teams that consistently achieve inclusive enrollment? (5) What concrete steps can be taken to develop a more inclusive, diverse network of trial investigators and leaders? The information presented in this manuscript reflects topics of discussion during this conference in response to these guiding questions.

We considered a number of resources to understand and apply the concept of underrepresentation, inclusion, and diversity in clinical research. We followed the FDA Center for Drug Evaluation and Research (CDER) approach which specifically highlights the gaps in representation in clinical trials for racial and ethnic minorities (Black or African American, Hispanic/Latino, American Indian/Alaska Native, Native Hawaiian, Pacific Islander, and Asian), women, and older adults [1]. This article will focus on strategies to improve inclusion among these groups. However, there are other populations, including sexual and gender minority groups, individuals with disabilities, and individuals with rare diseases who are also underrepresented in clinical research [5,6] and may face unique barriers to participation. Though a “one-size” approach certainly does not fit all, the strategies listed herein may be applicable to other populations underrepresented in clinical trials. During this conference, clinical trials were considered broadly according to the NIH definition. This manuscript highlights some strategies used in drug trials given the FDA and pharmaceutical industry representatives in attendance. However, the importance of diversity and inclusion applies to all of clinical research and many of these concepts can be applied to other elements of clinical research. Finally, in accordance with the American Medical Association guidance, racial and ethnic groups described in this article reflect race and ethnicity as a social construct, influenced by cultural, economic, and political forces with little biologic or genetic basis [7].

RESULTS: State of Diversity in Clinical Trials in the U.S.

In 1993, the U.S. Congress passed the NIH Revitalization Act [8]. This act called for increased inclusion of women and racial and ethnic minority groups in all federally funded clinical research. The purpose of this Act was to ensure the generalizability of results within these populations. Despite this guidance, these groups remain underrepresented in clinical research. For example, Black individuals represent only 8.2% of participants in clinical trials of pancreatic cancer, though they account for 12.4% of pancreatic cancer diagnoses in the U.S. [9]. Incongruities such as these exist across therapeutic disciplines. Within cardiovascular medicine, women, older adults, and individuals of non-white racial background were markedly underrepresented in randomized controlled trials [10] and the research used to generate scientific society guidelines [11,12]. Similarly, less than 5% of all NIH-funded studies of respiratory diseases published between 1993 and 2013 even reported inclusion of racial and ethnic minority groups [13]. Even among COVID-19 vaccine trials, only 58% reported race and 34.3% reported ethnicity, despite policies aimed at improving representation in these clinical trials [14].

Diversity in clinical research is highly valued for many reasons. Other than disease incidence in different segments of the population, there is no rationale for the population of clinical trial participants to differ systematically and continually from the demographics of the overall population or from the population affected by the condition of interest. For example, 2020 U.S. Census data show that the fastest growing demographic groups between 2010 and 2020 were Asian and Hispanic [15]. As the national population demographic shifts, so should the population of participants in clinical trials. This is important for scientific merit and validity. If the research sample does not represent the overall population or population affected by the condition of interest, the results may not be generalizable and could perpetuate mistrust in the scientific endeavor. Furthermore, minority groups in general experience poorer health outcomes in a variety of diseases [16]. Inclusion in clinical research is one way to address these health disparities. By intentionally including racial and ethnic minority groups, researchers may develop and refine more effective therapies.

Issues addressing the lack of diversity can be viewed from the standpoint of multiple stakeholders. From the regulatory perspective, the FDA recently published guidance on enhancing diversity of clinical trial populations [17]. This document provides recommendations for trial sponsors on how to increase enrollment of underrepresented groups by improving accessibility and broadening eligibility criteria. The FDA has also committed to transparency with annual publication of “Drug Trial Snapshots” reporting overall demographic inclusion data [1]. Federal funding agencies have likewise prioritized diversity and inclusion in clinical research. Examples of such efforts include the NIH-funded Community Engagement Alliance (CEAL) Against COVID-19 Disparities and the Coronavirus Prevention Network (CoVPN). CEAL seeks to remove barriers to participation by addressing misinformation and mistrust and building trust within racial and ethnic minority groups by partnering with community leaders, hosting events, and sharing best practices, with specific focus on the research on and public health response to the COVID-19 pandemic [18,19]. From the industry perspective, numerous barriers to participation have been identified, including lack of awareness of opportunities, resource

constraints, location and accessibility of sites and networks, mistrust, and complexity of study design. Strategic plans to overcome these barriers must focus not only on recruitment, but also retention, protocol compliance, and participant experience. Finally, from the academic perspective, stakeholders identified the importance of community engagement. In this regard, an initial crucial step is understanding how an academic institution is perceived within its local community, followed by assessing the needs of that community in order to develop a meaningful and mutually beneficial relationship.

Improving the inclusivity of clinical trials starts with engagement of diverse participants (Table 1). The first fundamental step is reaching out and offering opportunities for enrollment. A recent meta-analysis of clinical trials on cancer treatment found that more than half of the individuals who were offered trial participation agreed to enroll [20]. These participation rates did not differ significantly by racial subgroups—a similar proportion of Black and White patients agreed to join studies. Despite this willingness to participate, only 8% of individuals with cancer in the U.S. enroll in clinical trials [21]. This gap between apparent willingness to enroll and actual enrollment suggests that many patients may not even be offered opportunities to participate, yet they might be interested if the opportunity were made available to them. It is vital to improve awareness of clinical research among underrepresented groups, as there may be substantial untapped interest in participation.

Among various strategies to recruit minority groups, community engagement has emerged as one of the most effective [22,23]. Investigators with well-established community relationships are often the most successful at recruiting minority populations [24]. Community engagement does require up-front investment of time and resources. Researchers and institutions must spend time learning the needs of the community and invest resources in meeting some of these needs. The goal of this early investment is longstanding, mutually beneficial relationships that can be leveraged for both current and future academic and community partnerships, including engagement with clinical trials. Flexibility is also important as recruitment protocols that are co-designed with community input produce the best results [25].

As outlined in the Centers for Disease Control and Prevention (CDC) Principles of Community Engagement, there are various levels of community involvement in clinical research [26]. The most commonly applied level historically is unidirectional community outreach, in which information flows one-way from the researchers to community members. The peak of community engagement, on the other hand, is a multidirectional partnership, in which communities are involved in all aspects of the research project. This two-way flow of information facilitates bidirectional education. Researchers and institutions learn the needs of the community and the community learns the rationale and perspective of the researchers. As partners, both researchers and community groups are invested and take equal ownership of the design, implementation, and outcome of the study. These methods of community-based participatory research, which emphasize dialogue between researchers and community stakeholders, have been shown to improve recruitment of underrepresented minority groups [27].

Underlying these principles of community engagement is often the issue of trust. Although many individuals may be amenable to participation in clinical trials, others have expressed fear of mistreatment, exploitation, and unintended consequences when approached for trial participation [28]. These concerns are magnified in racial and ethnic minority groups [29,30], particularly in light of frequently cited past abuse in studies such as the Tuskegee Syphilis experiment and in the unauthorized use of Henrietta Lacks' cells, among other ethical violations [31,32]. Researchers and institutions must demonstrate trustworthiness to potential participants in order re-build these relationships. Earning trust requires time and effort, acknowledging past wrongs in scientific research, and a commitment to a future of humanizing clinical participation and the clinical research experience.

Accessibility is another key component of inclusivity in clinical trials. Research sites are not evenly distributed across the U.S. [33] (Table 2). Sites are generally clustered in urban areas and around large academic medical centers [34]. Because of this, many communities do not have easy access for study visits and follow-up. The physical distribution of research sites can hinder participation among underrepresented minority groups who do not live in close proximity to a clinical trial site. Often, due to familiarity and past performance, the same site networks are used in order to meet trial timelines and recruitment goals [21]. Expanding the lens of research operations to invest in non-traditional and novel types of sites allows new relationships to be formed with communities and community-based clinicians, thereby improving access in areas that have not traditionally been included.

Decentralized clinical trials may also improve the accessibility of clinical research. Decentralization refers to the conduct of studies outside of traditional brick and mortar facilities. Decentralized trials often also leverage digital health and telemedicine to extend the reach of investigators [35]. Though they may introduce some technological barriers where technology or high-speed internet access is limited, these trials can reduce geographic barriers to participation.

Decentralization need not always mean establishing new, dedicated clinical trial sites across the country, as such an approach may not be feasible due to cost. There is also value in leveraging infrastructure already in place within communities to increase participation. Victor et al. used networks of barbershops to improve blood pressure control among Black men—a group with the highest rates of mortality from hypertension-related conditions but among the lowest rates of physician interaction [36]. This randomized clinical trial not only recruited participants at Black-owned barbershops, but also delivered the intervention at these locations with the help of the local barber. This trial recruited more than 300 non-Hispanic Black men, with a retention rate of 95% in the intervention group [36]. This is an important example of "meeting participants where they are," by connecting with a trusted community member/partner (in this case, the barber) and delivering the trial in a familiar environment.

In addition to physical accessibility, it is also important to consider the make-up of the clinical research workforce. In addition to being underrepresented as participants in clinical trials, racial and ethnic minority groups are underrepresented among investigators in clinical research. Among 600,000 full-time faculty at academic institutions, less than 5% are African

American, 3% Hispanic, and 1% Native American, [37] with underrepresentation increasing among medical school faculty over time [38]. These proportions are even lower when examining those who submit applications for NIH funding [37]. Similar disparities exist among sexes. Only 17.9% of women were lead authors in oncologic randomized controlled trials between 2003 and 2018 [39]. Similarly, only 20% of the studies cited in heart failure guidelines contain female authors, with no change in the proportion of women in the first or last author position over the last two decades [12]. Investigators from underrepresented groups are often more effective at recruiting underrepresented participants. For example, the heart failure clinical trials that were led by a female investigator had a 50% increase in the proportion of female participants [12]. Diversification of the clinical research workforce may translate to improved diversity within trial populations.

Expanding the clinical research workforce not only involves the hiring of individuals from underrepresented groups, but also offering support and mentorship of their research endeavors at critical time points throughout their career development. One such effort from the American College of Cardiology (ACC) diversity and inclusion initiative offers a clinical trial training course targeted to women and racial and ethnic minority groups to foster their development as investigators [40].

In their guidance for industry, the FDA identified the use of digital health technology tools as a key strategy to enhance diversity in clinical trials (Table 3) [41]. Examples of digital health tools include electronic sensors or devices that detect and measure a physical or chemical characteristic, and then transmit that information to a study database. In their guidance document, the FDA suggests that such tools may make trial participation less burdensome for participants by replacing site visits with remote acquisition of real-time data [41]. By decreasing participation burden, use of these tools may enhance recruitment and retention of underrepresented groups.

Digital health technology is integral to the decentralization of clinical research, as these devices facilitate improved connection between participants and investigators. Decentralized trials using digital tools also allow for increased flexibility for participants. Individuals who may not be able to join a traditional clinical trial due to temporal or geographic barriers may be able to participate in this alternative format. Digital tools can also be used to increase engagement. Investigators and participants can connect with each other, conceivably at any hour of the day, through mobile applications and online platforms. Although these connections are virtual, they may help foster some meaningful communication and relationship.

Although digital tools are promising, they are most effectively employed when their strengths and limitations are considered. First is the issue of access. Although the majority of Americans own a mobile phone, internet access can be limited in rural areas [42,43]. Research platforms may not be compatible with all devices and may require a smartphone to operate. Individuals from low-income groups also may not have access to a private space to discuss confidential topics with healthcare providers and investigators. Second is the issue of digital literacy. Potential participants may have difficulty interacting with study material online and struggle to understand inclusion and exclusion criteria presented in a

digital format [44]. Digital literacy appears to track closely with overall health literacy and is often lower in older adults and those of lower socioeconomic status [45]. Because these disparities exist, there is a risk that primary reliance on digital tools could exacerbate issues of representation in clinical research rather than ameliorate them. Digital health technology is not necessarily a shortcut. Clinical trials using digital tools must be approached with the same best practices for inclusivity as all other clinical research endeavors. Investigators should continue to pursue community engagement around digital tools. Investigators should continue to seek stakeholder input to understand how these tools might be beneficial and understand what barriers might exist. When used conscientiously in this way, digital tools can help improve access and decrease participant burden, thus enhancing participant experience and increasing diversity in clinical trials.

Conclusion

Improving diversity in clinical research is an ethical and scientific imperative in order to ensure generalizability of clinical research results, reduce health disparities, and promote public health and equity in the U.S. Fostering inclusivity requires a multifaceted approach focused on understanding the multi-causal and complex nature of underrepresentation in clinical trials, building partnerships with communities, improving trial accessibility, and leveraging digital health technology. The actionable steps developed during this multi-stakeholder conference represent opportunities to improve representation of the U.S. population in clinical trials, understand and improve community engagement in clinical trials, and apply innovative means to enhance recruitment and retention, thereby facilitating better translation of clinical trial results into improved population health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Interests:

MDK is supported by an NIH T32 training grant (5T32HL069749-18). BPL reports employment by Evidation Health and consulting fees from Bayer Pharmaceuticals. RA reports employment by and might hold stock or stock options in Sanofi. UB reports employment by Boehringer Ingelheim. AB reports leadership or fiduciary role in Sickle Cell Thalassemia Patients Network, The Conscious Connect and the Wittenberg Institute for Public Humanities and Sciences. CK reports employment by and might hold stock or stock options in SiteBridge Research, Inc. RM reports grants and personal fees from Amgen, grants and personal fees from AZ, grants and personal fees from Bayer, grants and personal fees from Merck, personal fees from BI, grants and personal fees from Novartis, personal fees from Abbott, grants from American Regent, grants and personal fees from Medtronic, grants and personal fees from Zoll, personal fees from Boston Scientific, grants and personal fees from Cytokinetics, personal fees from Respicardia, personal fees from Roche, personal fees from Vifor, personal fees from Sanofi, personal fees from Windtree, outside the submitted work; and Received research support and honoraria from Abbott, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim/Eli Lilly, Boston Scientific, Cytokinetics, Fast BioMedical, Gilead, Innolife, Medtronic, Merck, Novartis, Relypsa, Respicardia, Roche, Sanofi, Vifor, Windtree Therapeutics, and Zoll. JS reports employment by Pfizer, Inc. GB is supported by R01-MD013493.

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Table 1.

Participant Engagement, Recruitment, and Retention: Building Partnerships

Actionable Steps
• Ensure participation is offered and advertised to a diverse population.
• Dedicate time to understanding the reputation of your institution within the local community.
• Assess the needs of the community with whom you are engaging up-front, and work to align the research protocol with those needs.
• Engage the community as a partner beginning with trial design and continuing through retention, protocol compliance, and dissemination of results.
• Build community engagement into budgets, timelines, and scopes of work.
• Continue partnership with community even after completion of the trial.

Table 2.

Site Networks and Research Infrastructure: Improve Accessibility

Actionable Steps
• Prioritize participant access and experience in trial design
• Consider decentralized methods to minimize geographic barriers
• Prioritize diversity in the clinical research workforce

Table 3.

Digital Health Technology: Enhancing Diversity and Reducing Trial Burden

Actionable Steps
• Leverage digital tools to decrease burden for clinical trial participants
• Offer digital alternatives to groups who may not otherwise be able to participate
• Ensure inclusive and equitable use of digital tools by assessing digital literacy and device accessibility among potential participants