The Importance of Diversity and Inclusion in Drug Development and Clinical Trial Conduct

The Journal of Clinical Pharmacology
2022, 62(12) 1475–1479

DOI: 10.1002/jcph.2151

Kenneth T. Moore, MA, MS, FAHA, Oliver Grundmann, PhD, MS, MEd, Otito Iwuchukwu, PharmD, PhD, MA, FCP, Natella Rakhmanina, MD, PhD, FAAP, FCP, AAHIVS
On behalf of the ACCP Public Policy Committee

Keywords
diversity, inclusion, drug development, clinical trials (CTR), clinical pharmacology (CPH)

The American College of Clinical Pharmacology (ACCP) strongly recommends that researchers and health care professionals across the care continuum be more active in regard to the need for a greater diversity of participants in drug development and clinical trials. This can be supported through active participation in their professional and academic institutions, societies, and local communities. Health care professionals should strongly consider actions of advocacy, mentoring, education, and volunteering to better inform all stakeholders regarding the need for a greater diversity of participants in clinical trials and the drug development process. As health care professionals, regulators, and researchers, we should strive to ensure our actions in the design, conduct, reporting, and communication of clinical research reflect the diverse needs of our communities.

Current State of Clinical Trial Diversity

The effort to enroll a greater diversity of participants in clinical trials is not a new endeavor, but it is one that has yet to fully succeed. While federal agencies, advocacy groups, and the pharmaceutical drug/medical device sectors are aligned on the importance of diversity in clinical research, the actions taken to date have produced, at best, a partial response from our communities within the United States. Some attempts have advanced this issue and provided significant gains in recent years. For example, based on a recent Food and Drug Administration (FDA) Snapshot Report of all New Drug Application and Biologics License Application approvals (N = 517 trials) between 2015 and 2019, Black or African American participation has increased in 9 of the 13 recognized therapeutic areas of clinical research.[1] Trials in these research areas had Black or African American enrollment that was ≥13% of the total trial, which is proportionate or better than the overall Black/African American population recorded in the 2015 US census.[1] Still, most trial participants across all 13 therapeutic areas were predominantly White (78%) and non-Hispanic (75%).[1]

Despite these efforts, some therapeutic areas still have a consistently disproportionate enrollment of White participants. When assessing the same Snapshot Report, trials conducted in cardiovascular, pulmonology and rheumatology, and neurologic diseases, White participants consisted of 90%, 84%, and 81% of the total enrolled populations, respectively.[1] While Black or African American participants made up 14% of the total participants enrolled in the neurology trials, Asians, Native Americans or Alaska Natives, and Hispanics or Latinos were well below the 2015 census rates.[1] In fact, Asians were consistently underrepresented in trials across all 13 therapeutic areas, ranging from only 1% to 4%.[1]

It should be noted that all racial and ethnic minorities were underrepresented in oncology and hematology trials. Underrepresentation remains a significant concern considering minority populations are more likely to be diagnosed with certain cancers and are more likely

Submitted for publication 31 August 2022; accepted 3 September 2022.

Corresponding Author:
Kenneth Todd Moore, MA, MS, FAHA, ACCP, Public Policy Committee, PO Box1758, Ashburn, VA 20146
Email: info@ACCP1.org

to die prematurely than White individuals.[2] This issue has prompted a new round of initiatives by federal health agencies, advocacy groups, and the pharmaceutical industry. For example, the American Society of Clinical Oncology and the Association of Community Cancer Centers, along with companies like Johnson & Johnson, Pfizer, and Walgreens, have all created initiatives and dedicated funds to improve diversity in clinical trials.[3] Additionally, the recently created 2022 FDA Guidance for Industry titled "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry" is aimed to address both the increasingly diverse US population and the Biden administration's Cancer Moonshot project.[4,5]

This recent FDA Diversity guidance, which the ACCP fully supports,[6] recommends that sponsors submit a diversity plan as part of the Investigational New Drug application as soon as practical during drug development and before conducting the pivotal trials.[5] Current FDA Commissioner Robert Califf, MD, publicly stated, "The US population has become increasingly diverse, and ensuring meaningful representation of racial and ethnic minorities in clinical trials for regulated medical products is fundamental to public health."[4] He further stated: "Going forward, achieving greater diversity will be a key focus throughout the FDA to facilitate the development of better treatments and better ways to fight diseases that often disproportionately impact diverse communities."[4] This new federal initiative is certainly timely considering the global attention placed on vaccine development to prevent COVID infections and recent findings that showed members of racial/ethnic minority groups and older adults living in structural and socially unequal communities were underrepresented in the clinical trials for approved vaccines.[7] Lack of trial participation by these underrepresented groups proved to be an important lesson learned from the severe acute respiratory syndrome coronavirus 2 pandemic. What was ultimately shown following the height of the pandemic was that the rates of infection and related mortality among minority members in these communities were up to twice that of White individuals.[8]

The Scientific and Ethical Need for Diversity in Clinical Trials

While these initiatives continue to gain support and are being implemented, it is important to better understand the critical need for diversity when conducting clinical trials. As mentioned, minority groups are frequently underrepresented in biomedical research, although they often carry a disproportionately higher disease burden. Having a trial population that is reflective of the racial and ethnic diversity within the population that will ultimately use the medical products helps to better understand the potential pharmacological, safety, and efficacy differences that may occur when used in a real-world setting.[9] Clinical trials that are constructed to reflect this diversity, lessen the need for extrapolation, would be more generalizable to the public, and would increase the likelihood of optimal therapeutic intervention.[9–11] Additionally, early adaptation of this strategy during the drug development process, ideally starting with phase 1 clinical pharmacology studies, could provide an initial understanding of potential differences between racial and ethnic groups long before initiating the pivotal phase 3 trial and regulatory submissions for approval.[9]

Both the frequency and severity of some diseases and the pharmacological activity, safety, and efficacy of some treatments have shown significant differences based on race and ethnicity. For example, Black patients tend to have higher rates of hypertension and chronic kidney disease, while Hispanic Americans have the highest prevalence of nonalcoholic fatty liver disease compared to other races and ethnicities. Native Americans are more likely to have metabolic syndrome, and Asians are at a higher risk for hepatitis B and cirrhosis compared to other racial and ethnic groups.[12] The incidence of multiple myeloma in Black patients is almost twice that observed in non-Hispanic Whites, yet this racial group made up approximately 1.8% of the total enrolled patients in the pivotal trial supporting the regulatory approval of ixazomib.[13]

Responses to various pharmaceutical agents can also be very different due to race and ethnicity. Angiotensin-converting enzyme inhibitors used for treating primary hypertension are less effective in Black patients compared to other racial groups.[9] Similarly, Asians have a higher incidence rate of adverse events when treated with carbamazepine, while Black individuals administered isosorbide dinitrate show improved survival compared to White individuals.[9] Finally, both Black and Hispanic individuals were found to be at greater risk for drug-related AEs when treated with the anticoagulant warfarin. These AEs ranged from thromboembolism, bleeding, and hospitalization to death.[1,13]

Ultimately, when clinical trials are designed to enroll those populations most likely to suffer from the disease in question, the subsequent results have a greater impact on the potential survival of the entire population. Clinical research in heterogeneous populations helps facilitate the identification of disease subtypes and allows for potential adjustment of the therapy, as needed.[9] From an ethical standpoint, diversity in clinical trial participation supports the principles of beneficence and justice for those racial and ethnic

populations that are disproportionately impacted by disease and socioeconomically disadvantaged.[14] A drug development program that is not inclusive of diverse populations fails to adequately serve the health needs of the society we serve as health care practitioners and researchers.

Recognized Barriers When Trying to Increase Diversity in Clinical Trials

While a logical argument for greater clinical trial diversity has gained global awareness and acceptance, there are well-established barriers that challenge its implementation in the United States. First and foremost is a general lack of trust. Our society is still in the process of healing the multiple historical wounds created from accounts of unethical behavior from individual physicians, academic institutions, and federally conducted research. This mistrust has a long history that encompasses the research of Dr. James Marion Sims in the 1840s when developing surgical techniques to repair vesico-vaginal fistulas in Black female slaves; the 40-year Tuskegee syphilis study in indigent Black farmers that began in the 1930s; the Willowbrook hepatitis studies in children with intellectual disabilities that occurred in the 1950s; and the Jewish Chronic Disease Hospital permitting cancer cells to be injected into otherwise healthy elderly patients with dementia without their consent in the 1960s, to name a few.[15] However, even beyond these terrible historical events, this lack of trust is further compounded by a lack of general scientific and low health literacy, language barriers, fear of negative family opinions, social stigma, and not seeing the value in clinical trial participation.[9,11]

Other barriers tend to be more logistical. Time constraints, financial burdens, child-care needs, limits with transportation, and lack of compensation tend to be barriers for all trial participants. However, these are even more challenging for those in socioeconomically marginalized communities, where more ethnically diverse populations may live and work.[9,11] Some barriers may be more artificial in nature and inadvertently created by those conducting the research. For example, many pharmaceutical industry sponsors repeatedly use the same research sites and investigators when conducting research. While this business model may provide better efficiency in meeting drug development goals, it limits diversity in trial location and participation.[8] While federally sponsored research is typically conducted at major medical centers that serve these diverse communities, these centers do not typically engage with community-based health care practitioners, which has the potential outcome of limiting the pool of racially and ethnically diverse participants.[10]

This last barrier mentioned plays a significant role. Community engagement in clinical research is lacking in most areas of the United States. Unfortunately, most health care practitioners have a lack of clinical trial training, awareness, and knowledge about the types of ongoing clinical research and the need for diverse participation. Local practitioners lack both the time and compensation for discussing trial participation with their patients, and many more fail to see the significant role clinical research plays in the overall care continuum.[10] Engaging local health care professionals is essential for establishing trusting relationships and creating transparency about clinical research. These local provider-patient relationships create an open dialogue to share knowledge about the importance of research and the benefits and risks of trial participation.[10]

Potential Strategies to Remove Existing Barriers in Clinical Trial Diversity

The following are some examples of potential strategies to overcome existing barriers in clinical trial diversity:

1. Enhance health care practitioner training in clinical research, bioethics, and best practices while also involving more community health professionals in the clinical trial process.

By enlisting more community-based health care professionals into research, investigators extend the overall reach, reduce recruitment delays, and enroll a trial population that better resembles the eventual users of the product if approved.[10] Through enhancing local health care practitioner education and training, stronger community partnerships are developed with critical community groups and leaders in both a transparent and effective manner that is more culturally appropriate.[11] This process also fosters the development of an ethnically diverse research team, thereby improving communication and rebuilding trust in the communities that are likely the most impacted by the disease states being researched.[9,12] Finally, establishing greater trust, understanding, and communication around medicine and clinical research within our communities will likely lead to greater diversity in future generations of those pursuing careers in health care and research. While this can be considered a longer-term strategy, it is one that should be strongly considered to ensure an eventual health care and research system that best reflects our increasingly diverse society.

2. Embrace novel clinical trial design and improve trial conduct.

Considering novel trial designs and improving how trials are conducted is another potential strategy to

break through these established barriers. Designs that are more patient-centric would likely improve both participant enrollment and diversity.[11] This can come in the form of adaptive and decentralized trial designs, in addition to incorporating model-based clinical pharmacology strategies as well as the earlier referenced use of real-world evidence to better inform and enhance drug development.[7] The sooner sponsors can apply these techniques within development, the more information will be known about the potential intrinsic differences in the pharmacological profile of the product and may also help limit the number of inclusion and exclusion criteria when conducting longer-term phase 2 and 3 efficacy trials.[9] Importantly, these actions have the potential to lower the barrier for trial entry and enhance diversity in the participant pool.

New technological modalities to improve data collection and monitoring should also be embraced. Remote data capture through wearable technology, virtual clinic appointments, telehealth, digital health technologies, mobile sample collection (when possible), and home health visits are just a few examples of solutions that may help enhance the enrollment of demographically and geographically diverse populations and reduce the logistical burden placed on participants.[9–11] In addition to addressing trial design and conduct barriers, sponsors should also address ethically sound compensation practices.[16] Payment in the form of either (1) reimbursement for expenses incurred as part of trial participation, (2) compensation for time and effort related to trial participation, and (3) incentive payments to encourage participation, retention, and study completion are all examples of reasonable strategies that are considered ethically sound if they do not cause undue inducement.[16]

3. Greater involvement and role of institutional review boards and research ethics committees to ensure trial diversity.

Institutional/Ethics review boards (IRBs) play a critical role in clinical research and have the authority to approve, disapprove, and require changes to all research being conducted at their institution. Their oversight of clinical trials starts before initiation and continues throughout the conduct of the trial to ensure the ongoing protection of participants. The specific requirement for IRBs can be found in Title 21, Chapter I, Subchapter A, Part 56 of the Code of Federal Regulations.[17] In short, each IRB should have at least 5 members with varying backgrounds and be "sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects."[17] Considering their importance in the research process, IRBs can play a greater role in ensuring trial diversity by maximizing the inclusion of understudied groups if it is consistent with the aims of the study.[14] Greater IRB monitoring through the recruitment/enrollment period can help ensure the population selected represents the demographics of the condition being studied.[14] Another requirement of this regulation is the need for a diverse review board, which should comprise different races, sexes, and professional backgrounds. By using ad hoc consultants, patient care advocates, and community representatives, an emphasis can be placed on the need for representation that is reflective of the communities the research is being conducted in.[14]

Regardless of the strategies employed, an effective and sustainable resolution to this issue will require a multifaceted approach. Enhancing trial diversity will ultimately require the involvement of all stakeholders working in collaboration. The various regulatory initiatives and guidelines enacted from 1993 to the present day have created the foundation for this change. However, the structure built on top requires the combined and continuous efforts of sponsors, IRBs, academia, advocacy and professional associations, scientific and medical publishers, regulators, and, most importantly, the actual health care practitioners and researchers.

4. Engagement with the community and patient advocacy.

While adequate funding for patient advocacy programs and community initiatives is always needed, it should not remain the only solution. Involvement of health care professionals and researchers familiar with clinical research and drug development are needed at every level of participation. Actively partaking in community events; engaging with local government officials, religious leaders, educators, and neighbors; or mentoring local health care professionals in the fields of bioethics and medical research can help broaden the overall health literacy of the community and increase their involvement in every stage of clinical research.

ACCP Call to Action

The ACCP strongly recommends that researchers and health care professionals across the care continuum increase their activity in institutions and companies, professional societies (such as ACCP), and local communities through advocacy, mentoring, education, volunteering, and participation to better inform our society about the importance of clinical research. This is the first step to facilitate an understanding of the need for greater diversity in those who conduct and/or

participate in the clinical trial process. Through our role as health care professionals and researchers trained in clinical pharmacology, we should strive to ensure that our actions, through the support of clinical study design, conduct, reporting, and communication of these trials, along with our engagement with local practitioners and their communities, reflects the diverse health care needs of our larger society.

Conflicts of Interest

K.T.M. is an employee and shareholder of Janssen Pharmaceuticals and declares no conflicts of interest.

Funding

No funding was received for this Position Paper.

Data Availability Statement

This will not be Open Access.

Disclaimer

The opinions expressed in this article are those of the authors on behalf of the American College of Clinical Pharmacology and should not be interpreted as the position of the entities or institutions at which the authors are employed.

ACCP Public Policy Committee

Mark Rogge, PhD, FCP; Sudhakar M. Pai, PhD, FC; Jean Michel Gries, PharmD, PhD, FCP; Michael J. Fossler Jr, PharmD, PhD, FCP; Bruce Gaynes, OD, PharmD; Douglas Greene, PhD, FCP; Manoj Jadhav, PhD, FCP; Parag Kumar, PharmD; Kenneth Todd Moore, MA, MS, FAHA; Joanna C. Masters, PharmD; Ahmed A. Othman, PhD, FCP; Lorraine Rusch, PhD, FCP; Ahmed Hamed Salem, PhD, FCP; Islam Younis, PhD, MSc, FC.

References

1. Lolic M, Araojo R, Okeke M, Temple R. U.S. racial and ethnic participation in global clinical trials by therapeutic areas. *J Clin Pharm Ther*. 2021;46(6):1576-1581.
2. Symes YR, Modell JG. What drug development sponsors, contract research organizations, and investigators can do to increase diversity in clinical trials. *J Clin Pharmacol*. 2020;60(3):281-283.
3. Caplan AL. Needed: a clearer explanation of why diversity in clinical trials is important. *First Opinion*. STAT. 2022; https://www.statnews.com/2022/06/23/needed-clearer-explanation-importance-diversity-in-clinical-trials/ Accessed August 12, 2022.
4. Al-Faruque F. FDA recommends sponsors plan to include race, ethnicity in clinical trial design. *Regulatory Focus*. 2022; https://www.raps.org/news-and-articles/news-articles/2022/4/fda-recommends-sponsors-plan-to-include-race-ethni#:~:text=FDA%20recommends%20sponsors%20plan%20to%20include%20race%2C%20ethnicity%20in%20clinical%20trial%20design,-Regulatory%20News&text=The%20US%20Food%20and%20Drug,investigational%20products%20to%20agency%20reviewers Accessed August 12, 2022.
5. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). 2022; Guidance for industry - Diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials guidance for industry.
6. American College of Clinical Pharmacology. Response to FDA docket No. FDA–2021–D–0789, Diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials, draft guidance for industry. https://accp1.org/pdfs/documents/FDA-2021-D-0789-0037_ACCP-Comments.pdf Accessed August 12, 2022.
7. Flores LE, Frontera WR, Andrasik MP, et al. Assessment of the inclusion of racial/ethnic minority, female, and older individuals in vaccine clinical trials. *JAMA Netw Open*. 2021;4(2):1-11.
8. Flores LE, Frontera WR, Andrasik MP et al. Assessment of the inclusion of racial/ethnic minority, female, and older individuals in vaccine clinical trials. *JAMA Netw Open*. 2021;4(2): e2037640.
9. Masters JC, Cook JA, Anderson G et al. Ensuring diversity in clinical trials: the role of clinical pharmacology. *Contemp Clin Trials*. 2022;118:106807.
10. Woodcock J, Araojo R, Thompson T, Puckrein GA. Integrating research into community practice - toward increased diversity in clinical trials. *N Engl J Med*. 2021;385(15):1351-1353.
11. Clark LT, Watkins L, Piña IL et al. Increasing diversity in clinical trials: overcoming critical barriers. *Curr Probl Cardiol*. 2019;44(5):148-172. Epub 2018 Nov 9. Erratum in: Curr Probl Cardiol. 2021;46(3):100647.
12. Editors: Rubina E. Striving for diversity in research studies. *N Engl J Med*. 2021;385(15):1429-1430.
13. Woods-Burnham L, Johnson JR, Hooker SE Jr, et al. The role of diverse populations in US clinical trials. *Med (NY)*. 2021;2(1):21-24. Epub 2021 Jan 9.
14. Strauss DH, White SA, Bierer BE. Justice, diversity, and research ethics review. *Science*. 2021;371(6535):1209-1211.
15. Lederer SE. The ethics of experimenting on human subjects. In: Baker RB, McCullough LB, eds. *The Cambridge World History of Medical Ethics*. Cambridge University Press; 2009: 558-565.
16. Bierer BE, White SA, Gelinas L, Strauss DH. Fair payment and just benefits to enhance diversity in clinical research. *J Clin Transl Sci*. 2021;5(1):e159.
17. Code of Federal Regulations. Title 21, Chapter 1, Subchapter A, Part 56 - Institutional Review Boards. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-56 Accessed August 12, 2022.