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Diversity in Clinical Trials Participation: A Life Sciences Perspective

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Introduction

Providing optimal care to all patients is an imperative that unites the various, interconnected parts of the medical field, from primary care to the pharmaceutical industry to the work of large academic medical centers. Over the past 30 years, there have been exceptional advances in care, treatment, diagnostics, and early identification of disease. Unfortunately, even with these many technological advances, addressing the importance of diversity has been lagging. Since the advent of clinical trials, recruitment has been largely centered on White populations. Although over 40% of the US population is currently comprised of ethnic and racial minorities,[1] quite often only 5 to 10% of clinical trial participants represent any minority population.[2] The disparity is striking and can also leave care providers with a detrimental lack of foundational information, not only with respect to what therapeutics might be most effective in minority patients, but also leave gaps and unanswered questions regarding potential adverse events and contraindications.

Although **over 40% of the US population** is currently comprised of ethnic and racial minorities , quite often **only 5 to 10% of clinical trial participants** represent any minority population.

Since the Food and Drug Administration's (FDA's) revised guidance on clinical trials diversity was issued in November of 2020, Trinity Life Sciences, with support from its Diversity, Equity and Inclusion (DEI) committee, has embarked on a more formal examination of the clinical trials diversity question in order to provide further insight on this issue to our clients and community. Through the first part of this work, which is described herein, we have summarized and provided context from a comprehensive literature review and primary market research effort driven by a life sciences perspective. Our focus for this initial work was to gather potential research topics from secondary research, then provide more depth to the issues through a well-rounded research sample of physician investigators, patients and clinical trial coordinators. The major tenets of this qualitative portion of our research have centered around clinical trial diversity providing a positive impact on:

- **Support of methodological stewardship.** Ensuring trials are well designed and include consideration of diverse-as-possible populations in all trials, plus special considerations for populations that are representative of persons who may be affected by a disease or impairment. As a multitude of post-market surveillance studies have shown, therapeutics often demonstrate amplified safety and/or efficacy signals once administered in a wider population. Genotypical and phenotypical differences among all individuals inherently require diversity to detect efficacy and safety signals, and for diseases that disproportionately affect minority populations, prioritizing their inclusion is paramount for determining true therapeutic effect
- **Accuracy and comprehensiveness of safety and Adverse Event (AE) reporting.** As different races, ages, and genders may react differently to different agents, it is prudent and necessary to be as inclusive as possible in clinical trials. Efforts to increase diversity are important to ensure there are no key differences in the way different populations respond that could be significant for on-label use

[1] US Census Bureau. "Racial and Ethnic Diversity in the United States: 2010 Census and 2020 Census." Census.gov, 14 Oct. 2021, https://www.census.gov/library/visualizations/interactive/racial-and-ethnic-diversity-in-the-united-states-2010-and-2020-census.html.

[2] The Editors. "Clinical Trials Have Far Too Little Racial and Ethnic Diversity." *Scientific American*, Scientific American, 1 Sept. 2018, https://www.scientificamerican.com/article/clinical-trials-have-far-too-little-racial-and-ethnic-diversity/.

- **Ensuring the patients who suffer from the disease are in primary focus.** Many diseases disproportionately affect certain racial groups more than others[3] (e.g., diabetes, sickle cell, cardiovascular conditions, Crohn's). In these cases, representation of the people most likely to be taking the medication is critical for accuracy of data and desired outcomes in clinical trials.
- **Social impact and partnership among historically marginalized groups.** Actively recruiting minority populations can help mend old wounds and build trust among minority participants. For example, African Americans have been historically wronged by atrocities in clinical trials in the past, and many are still wary of these situations occurring in present day. Fostering positive experiences can help break down the resistance to participation among others within this group.

Actively recruiting minority populations can help mend old wounds and build trust among minority participants.

Although many pharmaceutical companies and sponsors of clinical trials have adopted or increased their focus on diversity in clinical trials, preliminary market feedback is showing that pressure must be kept on this accelerator in order to overcome past inertia and inequities. In the following pages, Trinity Life Sciences outlines several emerging hypotheses and generally understood challenges regarding lack of minority trial participation, from a life sciences perspective. In addition, the research team has described herein specific drivers of increased trial participation as a result of recommendations from primary qualitative research findings.

> "Increasing diversity in research participation needs to be a priority. There need to be committees that will meet these needs and uphold these values. We need to keep up with numbers and statistics to see what efforts are working to recruit more diversity in clinical trials. This should be an ongoing effort."

[3] Drugs approved by the FDA can demonstrate differences in exposure and/or response across racial and ethnic groups. Ramamoorthy, A, et al. "Racial/Ethnic Differences in Drug Disposition and Response: Review of Recently Approved Drugs." *PubMed*, U.S. National Library of Medicine, 20 Jan. 2015, https://pubmed.ncbi.nlm.nih.gov/25669658.

Methodology

To understand the existing state of clinical trial diversity and the challenges trial administrators and participants have encountered, we employed a two-phased research approach. In the first phase, we conducted a comprehensive literature review to understand the current body of knowledge on clinical trial diversity. The literature confirmed the premise that clinical trial diversity continues to be a persistent problem across the US despite current efforts. Moreover, literature underscored concerns regarding fear of clinical trials among certain minority groups based on historical travesty, access and economical concerns such as time away from work, and lack of inadequate information and/or time to make decisions that could leave out treatment options, or concerns regarding placebo group placement and potential lack of personal benefit.

Methodology Overview

1. A comprehensive literature review was conducted to understand the current body of knowledge on clinical trial diversity. We utilized the findings from our literature view as the basis of the topics to explore in one-on-one interviews. Over 300 peer-reviewed journal articles were examined for this phase.

2. The primary market research was conducted using a semi-structured qualitative interview methodology. Multiple one-on-one, 60-minute telephone interviews were conducted with physicians, patients and clinical trial coordinators across the US. The sample included eight physicians across various specialties who have served as principal investigators for a clinical trial in the last five years, two clinical trial coordinators, and ten patients who have participated in a clinical trial in the last three years. Recruitment was intended to be as inclusive among a racially and/or ethnically diverse group of respondents as possible, with the most diversity observed among patient respondents

3. To gather a comprehensive understanding of the clinical trial experience, we interviewed physicians who are principal investigators in clinical trials, clinical trial coordinators, and patients who have recently participated in a clinical trial

State of Diversity in Clinical Trials

While diversity in clinical trials has increased to an acute focus for the healthcare industry, particularly among drug developers, the movement continues to be mired in a decades-long, slow, and piecemeal struggle. The first American policy to address clinical trial diversity was the NIH Revitalization Act of 1993, which required that all NIH-funded research must be inclusive of women and minorities.[1] Notably, this policy does not directly extend to non-NIH-funded research and including privately funded research by drug developers. Federal policy addressing clinical trial diversity remained relatively stagnant before the FDA issued an official guidance document in November 2020 on how to design clinical trials to be more inclusive of diverse populations. The FDA guidance document includes recommendations on how to enhance clinical

Underrepresentation in research subsequently leads to a sequalae of **negative impacts** on patients—impacting all aspects of healthcare, including social dynamics, healthcare utilization, and most importantly, outcomes.

trial diversity through eligibility criteria, enrollment, and trial designs. However, it is emphasized as guidance and not a strict requirement.[2]

Despite the enhanced guidance and ongoing efforts by trial sponsors and institutions, clinical trial diversity remains a challenge for academic- and industry-sponsored clinical trials, with industry-sponsored trials lagging farther behind in patient representation of minorities. In 2017, over 59,000 patients participated in clinical trials for 46 novel drugs approved by Center for Drug Evaluation and Research (CDER). Patient enrollment was overwhelmingly Caucasian, with White patients representing 77% of participants.[2] Similarly, in 2019, Pfizer released an overview of their clinical trial demographic breakdown; nearly 81% of clinical trial participants were White, while African Americans, Hispanics or Latinos, and Asian Americans comprised 14.3%, 15.9%, and 3.1%, respectively (multiple race responses were recorded and counted each time).[1] Beyond clinical trials, lack of diverse samples in research is pervasive. More than 80% of genome-wide association studies have been conducted among individuals of European descent. Hispanics or Latinos represent only 0.5% of those in genome-wide association studies.[4] Underrepresentation in research subsequently leads to a sequalae of negative impacts on patients—impacting all aspects of healthcare, including social dynamics, healthcare utilization, and most importantly, outcomes.

Qualitative Results: Barriers to Clinical Trial Enrollment and Completion in Minority Groups

Although the actual impact of barriers to participation is a complex question, the functional concerns can be attributed to several key themes: lack of appropriate, well-constructed support by the clinical trial sponsor, socio-economic barriers of participants, language or communication concerns not addressed, and frequency and complexity of clinical trial requirement demands from a time and events standpoint. While not all minority populations experience every barrier, nor do they experience to the same degree, by not addressing each barrier, trial sponsors may inadvertently deter ideal patient participants from enrolling and completing a trial.

Several patient respondents suggested having the ability to **speak with another patient** who had participated in a trial and sharing of their knowledge and advice could have persuaded them to pursue enrollment.

One of this study's directional findings suggests institutions or sponsors of clinical trials may lack robust patient engagement plans and therefore may fail to have the needed comprehensive discussions with patients regarding the clinical trial participation unless it's deemed clinically relevant. Of note, diversity in clinical trials tends to be more successful in trials where diversity is incentivized in a more targeted or personalized manner. One physician investigator noted that while the NIH requests more diversity in recruitment, sponsored trials may not be as strategically focused on the nuances or regional variations of incentives that could drive change. As a result, resources trial sponsors dedicate to patient engagement may lack a targeted or stratified focus on diversity, which squanders awareness and continues to miss opportunities to correct misconceptions about clinical trials that may deter patients

[4] Pan, Xingyi. "Lack of Diversity in Clinical Trials: The Problem and Potential Solutions." *Hopkins Biotech Network*, 20 Nov. 2020, https://hopkinsbio.org/academic/diversity-in-clinical-trials/.

from participation. It was also noted that these same privately sponsored clinical trials may be inadvertently limiting in their site selection unless there is direct intention of increasing diversity of patients.

Interestingly, there is a perception among the medical community that the priority placed on determining efficacy and other clinical endpoints coupled with desire for medical innovation compromise diversity in enrollment and participation. Physician investigators interviewed stated a strong motivation for participating in clinical trials is due to the proximity to innovation and chance to be "leaders in the field" and on the "cutting edge of medicine". Respondents also stated that other than inclusionary and exclusionary criteria in clinical trials, trial sponsor determined primary and secondary endpoints were key in helping to market the drug to demonstrate "decreased hospitalization, decreased health economics cost". In short, when incentives for more clinical criteria tend to outweigh any criteria that might exist for more diverse recruitment, sponsoring organizations may end up engaging in non-inclusive site selection. As a result of diversity criteria lacking equal emphasis, physicians may unintentionally recruit non-diverse participants in their clinical trials purely out of naivete without mal intent of excluding non-white populations in trial recruitment and participation. Furthermore, the lack of diversity of the clinical trial staff itself may be hindering further diversity in enrollment and participation. Some patients interviewed expressed more comfort with physicians and/or technicians throughout the trial who were of diverse backgrounds.

Often a topic of conversation among experts is that clinical trials lack diversity because of mistrust in the medical industry among minority patients. Similar to this observation, insights gathered showed African Americans cite institutional mistrust from generational trauma from the Tuskegee clinical trials. It is of note that although respondents mentioned Tuskegee frequently, other historical examples of medical abuse are noted, such as forced sterilization of Black, Latina and Native American women,[5] and the harvesting and use of HeLa cells without the knowledge or consent of the patient, Henrietta Lacks,[6] which are a still widely used human cell line in medical research. Potential clinical trial enrollees are therefore understandably concerned about the threat of hidden agenda or potential harm such as these sinister experiences inflicted in the past. Several physician respondents mentioned African American and Hispanic populations especially may hold disproportionately more mistrust in clinical trials due to potential medical abuse or lack of consent. Additionally, there may be other negative perceptions about the nature of research itself, such as the potential to be treated as a "test subject", which creates more hesitance and reluctance to participate, even with encouragement. Overcoming these deeply held reservations requires more time and effort to communicate effectively, provide a foundation for trust, and mitigate immediate and ongoing concerns.

Some patients also offered they may be less inclined to participate in clinical trials due to mistrust of their own physicians. More than one patient mentioned the necessity of searching for and finding clinical trials independently because they did not believe their own physician to be helpful in this regard, indicating a gap in communication, sensitivity, and awareness that needs to be filled. One patient stated that she researched an eczema clinical trial and preferred not to discuss it with either her dermatologist or primary care physician (PCP) due to lack of trust in their response or support. Other patients found avenues of learning about clinical trials from close family members, friends or by proactively researching online, with multiple patients citing Facebook as a main source of trial awareness and information. Several patient respondents suggested having the ability to speak with another patient who had participated in a trial and sharing of their knowledge and advice could have persuaded them to pursue enrollment.

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[5] Stern, Alexandra. "Forced sterilization policies in the US targeted minorities and those with disabilities—and lasted well into the 21st century". *IHPI News*, University of Michigan, 2020. September 23, 2020. https://ihpi.umich.edu/news/forced-sterilization-policies-us-targeted-minorities-and-those-disabilities-and-lasted-21st

[6] Wolinetz, Carrie D. and Collins, Francis S. "Remembering the Legacy of Henrietta Lacks". *Journal of the American Medical Association*, 2020; 324(11);1027-120. August 11, 2020. https://jamanetwork.com/journals/jama/fullarticle/2769506

Even when barriers to enrollment are overcome, patients may hesitate to follow through with a prescribed clinical trial program for reasons such as lack of additional information, incomplete answers to questions, lack of support, or even a misunderstanding of how clinical trials work and the necessary commitment to the process. Some may become overwhelmed from the complexity of the requirements, and if there is not access to a familiar or trustworthy person (member of community or clinical trial touchpoint), they may decline further participation. Other patients may have language barriers, and yet others may not feel comfortable with the many unknowns of clinical trials that necessitate an investment of time and energy not available to them under their current circumstances. Several physician respondents who led clinical trials cited Hispanic populations may have language barriers, which could require more time and resources such as interpreter services to provide thorough informed consent and ongoing support. Furthermore, informational requirements are frequently extensive as part of the trial enrollment process, which adds a confidentiality discomfort as some undocumented patients have concerns about maintaining their anonymity and wanting their personally identifiable information protected.

Clinical trial compensation remains largely insufficient to cover the income lost, transportation needs, childcare support, or other expenses, patients are less inclined to participate.

Rounding out this lengthy list of barriers is the considerations of socioeconomics. Many minority patients may face greater barriers to clinical trial enrollment and participation because of economic and circumstantial inequities that increase logistical barriers. For example, while some trial compensation programs offer gas cards, some patients do not drive. Other patients cannot reliably use public transportation due to distance or timing. Concerns regarding lost wages due to frequent medical absences necessitated by trial follow up visits, testing, and evaluations often deter otherwise willing participants. Indeed, many trials offer little support or compensation to balance the demands on the participants. Because clinical trial compensation remains largely insufficient to cover the income lost, transportation needs, childcare support, or other expenses, patients are less inclined to participate, and if they do enroll, they may be unable to complete complex or demanding trial schedules. Lack of flexible hours or deadlines for completion of trial requirements can also contribute to an inability to fully participate especially with the majority of medical appointment times occurring during traditional business hours of nine to five. Indeed, several participants mentioned patients who work off-hours shifts or more lengthy days would be deterred from participation. Couple these concerns with the initial time commitment needed to learn about the trial and the complete time commitment becomes unduly burdensome.

> "I think you need a diverse staff, doctors of color, specifically to help people of color with any issues they may face. You need to make sure it's not just general experimentation, but specific to the medical needs of the African American community. There needs to be a feeling of equity and using knowledge to help the community."

Study Recommendations: Near-Term Strategies to Improve Clinical Trial Diversity

Lessons Learned from the Impact of COVID-19

After discussing the barriers and implications underlying a lack of clinical trial diversity, this section will explore the low cost, high impact means to improving clinical trial diversity in the near term. To begin, one needs to look no further than the recent developments and adaptations in medical care prompted by the COVID-19 pandemic. While the world stopped to slow the spread of this virus, other diseases and conditions suffered by all patients continued to exist and progress. Out of a necessity to ensure continuation of trial participation, clinical trials sponsors and programs needed to adapt. Telemedicine was adopted for routine follow-ups that would have been otherwise conducted in the clinic. This has proven to be an effective strategy for minimizing exposure during the pandemic but can also realistically be an effective strategy to minimizing travel burden for future clinical trial participants.

Continuing the COVID-19 practice of allowing more widespread **telemedicine use may unlock greater participation** probability for potential candidates with minimized disruption to work schedules, and requiring no arrangements for childcare.

In any clinical trial, certain visits to the trial site are vital, such as when the patient receives treatment or lab work. However, this is not the case for all visits as some merely serve as check-ins with possibly the need for lab work. It is on days where trial protocol requires in-person evaluations despite lack of intervention where the travel and time burden of clinical trials truly manifest. If trial protocol requires more frequent interactions, continuing the COVID-19 practice of allowing more widespread telemedicine use may unlock greater participation probability for potential candidates with minimized disruption to work schedules, and requiring no arrangements for childcare. Further, collaboration between trial sites and community medical centers can reduce travel burden by outsourcing routine lab work to a more local setting without sacrificing the quality of the research. Finally, trial sponsors may also consider if the added insights from non-intervention-based office visits really provide that much more value to the study, thereby examining closely any opportunities to streamline the follow up process.

Additionally, COVID-19 practice insights revealed a barrier beyond simple travel time and costs, and that is the phenomenon of overcrowding in waiting rooms and clinic settings. To minimize contact points, several trial sponsors deployed traveling nurses to conduct check-ins in patients' homes. This certainly eliminated participant travel time much like telemedicine appointments would, but also maintained compliance due to the nurses' ability to provide visits outside of traditional business hours. Qualified nurses could also address the need for interventional monitoring such as blood draws, blood pressure and weigh-ins. When combined, telemedicine, clinic collaboration, reduced non-intervention appointments, visiting health professionals, and flexible hours could work to increase both accessibility and compliance by providing a more accommodating patient experience.

Enhancements to Trial Design

1. Beyond Eligibility Criteria

Beyond considerations as a part of trial eligibility, clinical trials can be technically limiting in the form of language barriers that prevent otherwise eligible patients from enrolling and participating. Sponsors and trial sites can better adapt to serve the needs of their communities by having adequate resources prepared for non-English speakers. This process should be a straightforward solution as clinics in predominantly Hispanic areas, by example, should already be able to meet the needs of a Spanish-speaking patient. Rather, the onus lies with trial sponsors in making such translated materials readily available as well as then the clinic to make such a request.

Health insurance status provides another barrier that excludes otherwise medically eligible patients. The cost of the drug in question is usually covered by clinical trial sponsors, however, other ancillary costs may arise. For example, a patient may be charged for the physician consultations or even for receiving the approved standard of care as part of the control group. Insured patients are insulated from such costs due to a provision in the Affordable Care Act requiring coverage for such routine costs in clinical trials, but uninsured patients may be excluded outright due to adherence concerns.[7] In isolation, support for the uninsured by trial sponsors will not ensure participation equity, however, it may be able to close the gap as in a 2021 report, the Kaiser Family Foundation reported that 26% of Hispanic-Americans ages 19 to 64 are uninsured.[8] We would be remiss, however, if we did not call attention to an ethical concern of expanding participation in this manner. Eventually, a situation would arise whereby an uninsured patient would receive treatment as part of a clinical trial but would then be unable to afford it once approved. In keeping with the scope of this paper, we do not have further commentary on such matters beyond mention of it as a potential outcome.

Trial site physicians and coordinators interviewed cited disease duration as an area for improvement in expanding trial access. The broad goal of any trial or scientific research is to test efficacy and safety under as objective and consistent conditions as possible. In late-stage clinical trials, inclusion and exclusion criteria work in tandem to ensure that only the patients in which the drug would benefit are recruited. This patient selection process sometimes takes the form of criteria based on a minimum disease duration. Used as proxy for disease progression and mitigation for possible misdiagnosis, this type of inclusion/exclusion clause was noted as restricting otherwise medically sound patients from enrolling in trials. Especially in underserved communities, early symptoms of disease can go unnoticed, and diagnosis delayed due to many reasons, including a lack of healthcare access. An example of late detection is especially prevalent in the disparity of timeliness of breast cancer diagnosis between African American and Caucasian women.[9] As such, it is our view that minimum disease duration (or time since disease resolution) should be removed in favor of more clinical methods of determining disease progression/status whenever possible. Taken together, these important trial design modifications can unlock a broader eligible patient population in striving towards more representative clinical research.

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[7] ASCO. "Affordable Care Act Provision Requiring Insurance Coverage of Clinical Trials." *American Society of Clinical Oncology*, 2014 American Society of Clinical Oncology, 2014, https://www.asco.org/sites/new-www.asco.org/files/content-files/research-and-progress/documents/faq-clinical-trials-coverage-statute.pdf.

[8] Artiga, Samantha, et al. "Health Coverage by Race and Ethnicity, 2010-2019." *KFF*, 16 July 2021, https://www.kff.org/racial-equity-and-health-policy/issue-brief/health-coverage-by-race-and-ethnicity/.

[9] Maly, Rose C, et al. "What Influences Diagnostic Delay in Low-Income Women with Breast Cancer?" *National Center for Biotechnology Information*, 2011, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3163388/pdf/jwh.2010.2105.pdf.

2. Site Selection

Improved trial design can certainly better enable a wider net of patient recruitment, but site selection ultimately determines where those nets are cast. Clinical trial coordinators and physicians note that site selection is an insulated system. Staff capabilities and the physician's capacity to handle the workload are certainly factors, but the scope of options is restricted to sites with which the sponsor has had previous experience. Such a process is not conducive to increasing diversity in clinical trials as these sites are often in well-resourced communities that serve a predominantly White patient population. To cultivate a more representative patient sample, clinical trial sponsors must broaden their site search to include clinics that may not have previously been involved in trial research but are well-equipped to do so – specifically those located in minority communities. Doing so may require more upfront involvement by the sponsor than re-selecting existing sites in their sphere, but meaningfully expands the patient pool in the long run. This is not to say that the system of choosing sites need be completely overhauled. Rather, it is a suggestion that the list should be examined in aggregate and expanded or modified periodically for the sake of more robust and generalizable research.

Clinical trial coordinators and physicians note that **site selection is an insulated system**. Staff capabilities and the physician's capacity to handle the workload are certainly factors, but the scope of options is restricted to sites with which the sponsor has had previous experience.

3. Patient Outreach and the Importance of an Accessible and Relatable Touchpoint

Modified trial designs may expand potential patient populations, but patients still prefer an initial touchpoint to spark interest in any given trial. Patients are generally recruited through physician referral, and this is unlikely to change. The following considerations, however, can empower patients to ask their physicians about participating in specific trials and potentially reach those who do not visit their physicians as regularly. Patients we spoke with were actively engaged in support groups on social media platforms like Facebook, where they found supplementary advice on managing their day-to-day lives with their medical conditions and received exposure to advertisements or postings to raise awareness of clinical trials. Patients may be more receptive to this type of outreach, especially when posted directly by the clinical trial coordinator, as it is received as more personalized when compared to a general online advertisement. Similarly, referred patients may be more likely to enroll in a trial once recruited if the clinical trial coordinator represents and understands the surrounding community. Such a connection will instill comfortability and reinforce the notion that the patient is a person and not a test subject. It is of note that individuals with lower socioeconomic status may not have access to technology that would allow them to research clinical trials, access Facebook, or participate in online support groups, which would require more efforts through physical community locations or other in-person forms of outreach.

Additionally, clinical trial coordinators suggested pairing the targeted recruitment with broader canvassing in high-touch locations such as grocery stores and public transit stations. Though such approaches may have a lower proportionate target identification rate, the rationale holds that given broader mistrust of medicine in underserved communities, when patients do not engage in the medical community as frequently, limiting first contact to a medical location only makes physician referral less likely. Such patients would benefit from the additional exposure, especially when it speaks to their specific condition and community. Unprompted, this hypothesis

was verified by our patient sample who mentioned a desire to help other fellow patients as a driving motivation behind their clinical trial participation. In this manner, outreach becomes community-wide, and "normalizes" exposure to clinical trials in a more informal context. In-person contact and communication with persons of similar ethnicity or race allows for greater opportunities for successful outreach.

4. Communication Strategies

Perhaps the easiest strategy to implement in the near-term is improved communication. This may not directly increase clinical trial enrollment immediately, but it can certainly ensure a more positive patient experience and greater acceptance of trials as a potential option. Study findings suggest patients also seek greater transparency over the course of a trial, suggesting that communication should not end once a patient has enrolled in a clinical trial and is actively participating. Certain clinical trials may last years, and patients can grow less motivated and disconnected over time if not appropriately engaged. A suggestion is for sponsors and trial sites to continue communicating the rationale behind the design throughout the trial. Part of this communication can

Sponsors and trial sites should **continue communicating** the rationale behind the design throughout the trial. Part of this communication can reinforce commitment as patients want to feel that the burden of continued appointments is logical and worth the potential benefit they can experience.

> "We need to educate the patient about their disease condition and why it is important to participate. Some don't understand the severity of their condition and lack of awareness that there could be any meaningful outcome. You need to tell them that this is important for the community. For example, we are finding that in ethnic groups there is higher rate of complication, of issues coming back, so we need to understand why it's coming back in your specific population. There is an importance to enrolling patients from a diverse background. Doctors need to be open and be a champion in our institutions. We need to make diversity a priority both for investigator and participants."

reinforce commitment as patients want to feel that the burden of continued appointments is logical and worth the potential benefit they can experience (or the ways in which accumulating knowledge will help others suffering from their condition in the future). To be clear, the benefit communicated does not necessarily need to be a direct benefit of efficacy but should employ some positive reinforcement and gratitude for the investment of their time. In-line with our comments in the earlier Patient Outreach section, we also recommend communicating the significance of the trial to their broader community of friends, family, and neighbors who may be suffering under the same condition. A community-based approach to encouragement can be especially motivating for patients who express concerns about potentially receiving the placebo as no matter the intervention group, patients can feel part of something bigger than themselves.

In addition to positive patient-provider communication, we encourage connecting patients to one another to foster an added level of mutual support. Whether one-on-one or in a group, connecting patients in clinical trials to each other can work to inspire and motivate in the same way advocacy-based and grassroots patient support groups do on social media. Enhanced support can have the pragmatic effect of preventing patient drop-out over the duration of the study since patients have outlets to vet concerns and experienced peers who can truly relate to their experience and offer tips for day-to-day management and encouragement.

5. Enhanced Financial Support

Patients interviewed in this study were more interested in cost-neutral reimbursement as opposed to generally increased compensation. They unanimously indicated their motivation to participate in trials was directly attributed to the opportunity to improve their condition, not from a consideration of remuneration. Thus, it is our belief that simply increasing compensation will not boost enrollment for underserved patients. Compensation measures can be optimized to alleviate the financial and logistical burdens that often come with participating in clinical trials. At a minimum, clinical trials should be cost negative for patients, but it is likely many current reimbursement models may miss broad swaths of attributable expenses by not clearly thinking through unique or specialized needs of different study participants. As the example used previously, sponsors often offer compensation or reimbursement for fuel, but this is only relevant for patients who own a car. To account for the variety of patient circumstances, a wider transportation package should be offered that incorporates, within reason, everything from fuel to mass transit to even taxi services and Uber or Lyft services. Certain treatments like induction chemotherapy require either monitoring for adverse events or several administrations in a short period of time. For patients who live far from the trial site, traveling back and forth frequently while battling the physical and emotional toll of the ordeal of cancer is unfeasible. Discussed in the context of COVID-19 changes, telemedicine and traveling nurses can also be deployed to ensure access to check-ins before nine or after five, preventing lost wages for patients who work in hourly positions. While these measures individually or in combination require additional investment, more effective examination of investment levels can optimize how readily clinical trials are recruited and how well patients are retained for the duration of the study.

At a minimum, **clinical trials should aim to be cost-neutral for participants**. It is likely many current reimbursement models may miss broad swaths of attributable expenses due to lack of understanding of socioeconomic differences among participants.

The Future: Broader Institutional Changes for Greater Progress

The aforementioned suggestions for more immediate impact are certainly important pieces of the puzzle to be solved, but longer-term solutions are also needed to encourage increased participation among minorities and keep clinical trial diversity at the forefront of scientific research. Racial disparities in health, especially among Whites and Blacks, continue to increase year over year.[10] Today, Black Americans continue to bear a disproportionate disease burden in both morbidity and mortality.[11, 12] Latino and Asian Americans also suffer from lack of cultural support and visibility of representation. Now, more than ever, it is important to consider how the stark lack of clinical trial diversity contributes to these healthcare-related disparities.

In addition to changes such as cost considerations, eligibility criteria, and patient outreach, policy changes among trial sponsors and trial sites need to be re-invented and implemented. In order to better measure suspected efficacy and safety of treatments in development, clinical trial populations need to accurately represent the array of patients suffering from the disease. Though not an easy challenge to address, there are several strategies to achieve an accurate portrayal of disease demographics. However, this cannot be accomplished without coordinated efforts of clinical trial sites and overseeing regulatory bodies or sponsors.

Though these solutions will take time and additional costs to implement, they will ultimately achieve a more equitable healthcare sphere with better, more predictable outcomes. Only with these institutional changes, be it policy, education, or messaging, will we achieve a sustained market impact long-term.

1. **Advertisements and Media Campaigns**

   Earlier, we outlined the impact of institutional mistrust among patients. Several physician respondents mentioned African American and Hispanic populations have disproportionately more mistrust in healthcare institutions and professionals, which significantly impacts their willingness to participate in clinical trials. Solutions posed include hiring clinical trial coordinators who represent and understand the surrounding community. Recruitment via this type of outreach establishes comfortability and reinforces the notion that the patient is a person and not a test subject. This can be taken one step further by increasing the level of racial, ethnic, and gender diversity in pharmaceutical company advertisements. By including a diverse group of individuals in advertisements, pharmaceutical companies not only express their commitment to equal representation, but also increase comfortability and trust in communities who have historically not been included in clinical trials. The consideration that "representation matters" extends to the micro-environment of trial participation.

   In the past few years especially, several pharmaceutical manufacturing companies have begun promoting more inclusive media. For example, Pfizer launched an ad campaign in April 2021, titled "Undo Underrepresented." This televised commercial spot highlights the need for people of all backgrounds to participate in clinical research

[10] Mays, Vickie M, et al. "Race, Race-Based Discrimination, and Health Outcomes Among African Americans." *Annual Reviews*, 5 Sept. 2006, https://doi.org/10.1146/annurev.psych.57.102904.190212.

[11] Centers for Disease Control and Prevention (CDC). "Health Disparities Experienced by Black or African Americans--United States." *MMWR. Morbidity and Mortality Weekly Report*, U.S. National Library of Medicine, 14 Jan. 2005, https://pubmed.ncbi.nlm.nih.gov/15647722/.

[12] Williams, David R. "African American mental health: persisting questions and paradoxal findings." Afr. Am. Res. Perspect 2 (1995): 2-6.

and provides a link to easily access Pfizer's clinical trials.[13] Promotional campaigns like this serve a three-fold purpose. They can inform minority populations about the option to enroll in clinical trials, they provide a direct and accessible entry point to these clinical programs, and also provide visual representation of peers and patients who more accurately depict their own situations and concerns. Addressing these issues more frequently with accuracy and sensitivity will help overcome concerns that have prevented minority populations from participating in clinical research in the past.

To note, this example advertisement campaign launched on several platforms, including digital display advertising and social media. This multi-channel media approach ensures that the messaging and imagery is accessible and easily viewed by as many individuals as possible, regardless of where they may be getting their information. As mentioned earlier, many patients interviewed were actively engaged in support groups on social media platforms. As a result, replicating campaigns on social media sites may help draw awareness to the possibility of participating in clinical trials. This broad-reaching communication may also be effective in outreach to underrepresented groups or under resourced regions where access to healthcare is limited or patients are wary of healthcare options.

2. Representation in Pharmaceutical Company Boardrooms

The majority of the top 20 pharmaceutical companies have created initiatives within the past couple of years to narrow the disparities in clinical research and clinical trial enrollment, in sharp contrast to historical lack of attention to the issue. In 2020, the Pharmaceutical Research and Manufacturers of America (PhRMA) put forth the "first-ever, industrywide" principles to provide guidance and information on diversity in clinical trial participation. Multiple pharmaceutical companies have also undertaken a decentralized effort to address concerns at a local/regional level. For example, the Bristol Myers Squibb Foundation and National Medical Fellowships launched program to help increase diversity and inclusion in clinical trials. Other companies are initiating or expanding partnerships to drive research in and improve diversity in clinical trial participation. Janssen recently expanded its partnerships to improve clinical trial design, including diversifying clinical trials. Programs like these will certainly help increase incentives to focus on diversity, but in order to instill minority populations with a sense of trust in clinical research, it is also necessary to increase diversity at the top rungs of pharmaceutical boards and within leadership teams. By prioritizing diversity among leadership, minority individuals will recognize that they are represented at the highest decision-making levels and may even gain reassurance that their communities are being considered of high importance in the drug development and the execution of clinical research. Visibility and representation among leadership is yet another important step to increase trust among individuals who still remember the horrors of the Tuskegee trials as well as individuals who fear being represented as a test subject rather than as an individual.

To support representation on a decision-making board, first pharmaceutical companies would do well to employ a specific individual or team dedicated to recruitment and hiring of diverse leadership. This investment and prioritization ensure that diversity, equity and inclusion efforts are kept at the forefront, with dedicated individuals working towards its success. It additionally ensures that the appropriate time, energy, and resources can be allocated toward meeting goals, rather than simply adding this as a task onto a set of ongoing responsibilities. Notwithstanding existing efforts to promote diversity in general within industry, these additional efforts will also help focus on equitable care provision and research diversity, with the goal of instilling trust as well as addressing diversity needs.

[13] Bulik, Beth Snyder. "Pfizer TV Ad Aims for Clinical Trial Diversity, with a Special Invite to the Black Community." *FiercePharma*, 30 Apr. 2021, https://www.fiercepharma.com/marketing/pfizer-tv-ad-addresses-health-inequities-clinical-trials-highlighting-new-hub-for-drug.

In addition to establishing more diverse boardrooms, we encourage pharmaceutical manufacturers to consider including their own diverse leadership team members in forms of public outreach, rather than just limiting diversity communications to the corporate environment. In doing so, manufacturers take another step to make sure that minority individuals are not simply represented, but included, visible and valued. This additional level of inclusivity may help build trust and recognition among various communities, ensuring that representation within leadership endorses advocacy and underscores a new era where diversity prevails in healthcare.

3. FDA and Sponsorship Policy Changes

Although the majority of our recommendations have focused on patients and pharmaceutical companies, diversity in clinical trials cannot be accomplished without coordinated efforts of clinical trial sites and overseeing regulatory bodies or sponsors. In the United States today, Black Americans makeup about 13% of the population. However, they make up only about 5% of clinical trial participants. Hispanic and Latino patients face an even larger disparity in representation. While they make up about 19% of the US population, they constitute only about 1% of clinical trial participants.[14] Despite these disparities in representation, the FDA has not instituted any minimum requirements around representation.

In order to better measure suspected efficacy and safety of treatments in development, clinical trial populations need to accurately represent the array of patients suffering from the disease. As such, we recommend the FDA institute specific policy requirements on representative recruitment for clinical trials. Ideally, these policy changes would not only reflect the makeup of the general population, but also consider the racial, ethnic, and gender makeup of the specific disease. For example, in 2018, racial and ethnic minorities made up about 87% of all reported cases of tuberculosis.[15] In the US specifically, non-Hispanic African Americans accounted for roughly 20% of reported tuberculosis cases nationally. At the time, non-Hispanic African Americans made up only 13% of the US population.[13] If a trial were to be conducted on a tuberculosis treatment, this racial health disparity should be considered, with recruitment skewed more heavily toward the non-Hispanic African American population. This would more accurately represent how a treatment would likely work in a real-world setting, since the patient population would be more accurately represented in trials.

One consideration of this requirement is that it is likely to make clinical trial recruitment slower and more onerous, potentially stretching out the timelines to reach medication approval. As a result, we recommend pairing this guidance with the other solutions we've posed, to speed up recruitment and feasibility of this suggestion. Additionally, it may be helpful for the FDA to have a centralized database where patients can sign up for clinical trial consideration as soon as they are diagnosed with a condition. This would help doctors to reach patients more easily and potentially target recruitment to specific racial, ethnic, or gendered groups who are still needed to meet these FDA requirements.

[14] Pfizer. "Diversity in Our Clinical Trials." *Pfizer*, https://www.pfizer.com/science/clinical-trials/diversity.

[15] Centers for Disease Control and Prevention. "African Americans/Blacks." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 14 Sept. 2020, https://www.cdc.gov/nchhstp/healthdisparities/africanamericans.html.

4. Communication and Educational Resources

We previously recommended communicating the significance of the trial to their broader community of friends, family, and neighbors to help patients remain motivated to continue in a clinical trial. However, this can be taken even a step further to motivate patients to enroll in a trial in the first place.

Patients in our research noted that although they may not trust healthcare practitioners, they often look toward other community leaders for guidance. For example, certain community members may share a personal, trusting, relationship with their pastor, social worker, or teachers. Enlisting these individuals to speak about the importance and impact of clinical trials and/or their own personal experience with trials, can help instill confidence in research. In particular, individuals who participated in clinical research noted that they were particularly motivated by altruistic aspects (the ability to help future individuals with the same condition), real-world data (showing the lack of minority participation in research), as well as education and representation (increasing minority participation in research and learning how medications can affect their particular group).

Additionally, because of the long-standing, trusting relationship with these community leaders, individuals would be able to address any concerns they have, and feel confident in the answers they receive. For example, Black individuals may speak about the trauma caused by the Tuskegee trials, English as a Second Language (ESL) learners would be able to ask about the trial in their native language, and undocumented patients would be able to confirm that they would be provided privacy and confidentiality around their immigration status. It is important to ensure that individuals entering into a clinical trial feel supported and heard. The practices and recommendations described in this paper are meant to create a better patient understanding of clinical research, improve patient-physician relationships, and increase overall confidence in clinical trials.

Conclusion

Increased focus on clinical trial diversity can not only improve patient trust, but also make results more generalizable to broader populations, thereby improving the relevance and reliability of the study. Despite efforts to help bridge the vast diversity gap in clinical trials, challenges persist and therefore trial sponsors must continue the breadth, depth, and intensity of any and all current efforts in order to affect meaningful change. Even with current programs and recent guidance updates, research sponsors can implement additional near-term strategies to improve clinical trial recruitment diversity, including enhanced communication efforts, targeted funding to decrease barriers to participation, and identifying point-persons to help promote confidence and answer in-depth questions, placing potential participants at greater ease. Among these suggested strategies, addressing barriers may have the greatest potential, but requires support, cooperation and direct engagement between trial sponsors and clinical trial site administration.

This renewed and sharpened focus on diversity in clinical trial participation holds promise in affecting tangible change within research and may even go a long way towards increasing trust within the medical community. While high-profile investments designed to understand and improve clinical trial diversity are important to addressing the gap, a multi-pronged approach with a combination of targeted, local, and individually prescribed support will be necessary. If deployed consistently, these more tactical changes at the individual clinical trial level as well as more broadly can have the potential to have significant impact on recruiting and maintaining diverse populations in clinical trials.

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