Understanding The Rationale And Potential Barriers To Diversity And Inclusion In Clinical Trials

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Why Now?

The importance of diversity and inclusion in clinical research is nothing new, however the coronavirus pandemic heightened the awareness of the issues that may arise when communities impacted by the disease or virus are underrepresented in clinical trials. As researchers raced to develop vaccines, industry discourse emphasized the importance of involving the people who needed them the most.

Another factor stoking more recent interest in diversity and inclusion is the FDA's issuance of new guidance in November 2020. The FDA publication offers recommendations for making clinical trials more inclusive of multiple populations and specifically for ensuring that the people participating in trials represent the populations most likely to use the investigational product once approved. The guidance considers demographic characteristics of study populations (e.g., sex, race, ethnicity, age, location of residency) as well as non-demographic characteristics of populations (e.g., patients with organ dysfunction, comorbid conditions, disabilities, those at the extremes of the weight range, and populations with diseases or conditions with low prevalence).

Growing consciousness of health inequity and other social injustices has also likely propelled diversity to become a priority in clinical research. Consideration during drug development has always been given to the populations for which a drug is intended, but the difference now is that if it is not done adequately, there may be regulatory ramifications – if not immediately, then potentially down the road. It is expected therefore that diversity and inclusion will continue to be a focus of the clinical research community for the foreseeable future.

Examining how the field of clinical research approaches diversity and inclusion gives us a baseline understanding upon which we can build as we continue to make necessary changes for improvement into the future.

To take this first step we need to understand why this is so important and explore the potential barriers to accessing underrepresented subgroups.

Underrepresentation Of Disease-appropriate Subgroups In Clinical Trials

Despite the potential complexities of incorporating diversity in clinical studies, it is important to do so because distinct populations have been known to respond differently to treatments. For example, patients with different racial and ethnic demographics have been found to respond differently, age does impact organ development and function, and weight can have an influence on drug distribution in the body.

Predilection to specific diseases

One example showing the exclusion of disease-appropriate subgroups can be seen in oncology. Some racial minorities can have equal or higher cancer rates compared to the population as a whole. For example, in 2020, the American Association for Cancer Research reported that African Americans have 1.5 times the incidence and twice the death rates from prostate cancer compared to any other race or ethnicity. While prostate cancer is a dramatic example and other cancers have different incidence rates, it is clear that cancer treatment is particularly relevant to racial minorities. However, in that same year, only an estimated one percent of registered cancer clinical trials were directed toward racial and ethnic minority populations, and only a third reported race and ethnicity in trial results.[1]

Gender-based differences

It is scientific fact that women process drugs differently than men, which can affect treatment outcomes and the incidence of adverse events. Gender-based differences have been found in drug absorption, distribution, metabolism, and elimination.[2]

There have been documented instances which have shown how problematic this can be, if not addressed correctly. It is estimated that only half of clinical trials perform gender-based analysis and only 35 percent conduct proper subgroup analyses. This can result in misleading conclusions, reduced external validity, distrust of the trial process, and consequences for women's health.

For instance, the results of a digoxin trial were published in 1997, demonstrating positive outcomes. However, a few years later, in 2002, Rathore *et al.* repeated the same study with the addition of an analysis based on gender. The results were identical for men, but showed that digoxin significantly increased mortality among women, and the drug-associated reduction of hospitalizations for heart failure was less.[3]

Barriers To Accessing Disease-appropriate Underrepresented Populations

Social determinants of health

A number of barriers can make it difficult for marginalized populations to take part in clinical trials. One useful schema for looking at these barriers is data on the Social Determinants of Health (SDOH) – the environmental conditions that impact people's health and quality of life. These can be broken into the five domains: economic stability, education access and quality, healthcare access and quality, neighborhood and built environment, and social and community context. SDOH are often out of individuals' control, and can include features such as language, neighborhoods, racism, and discrimination.

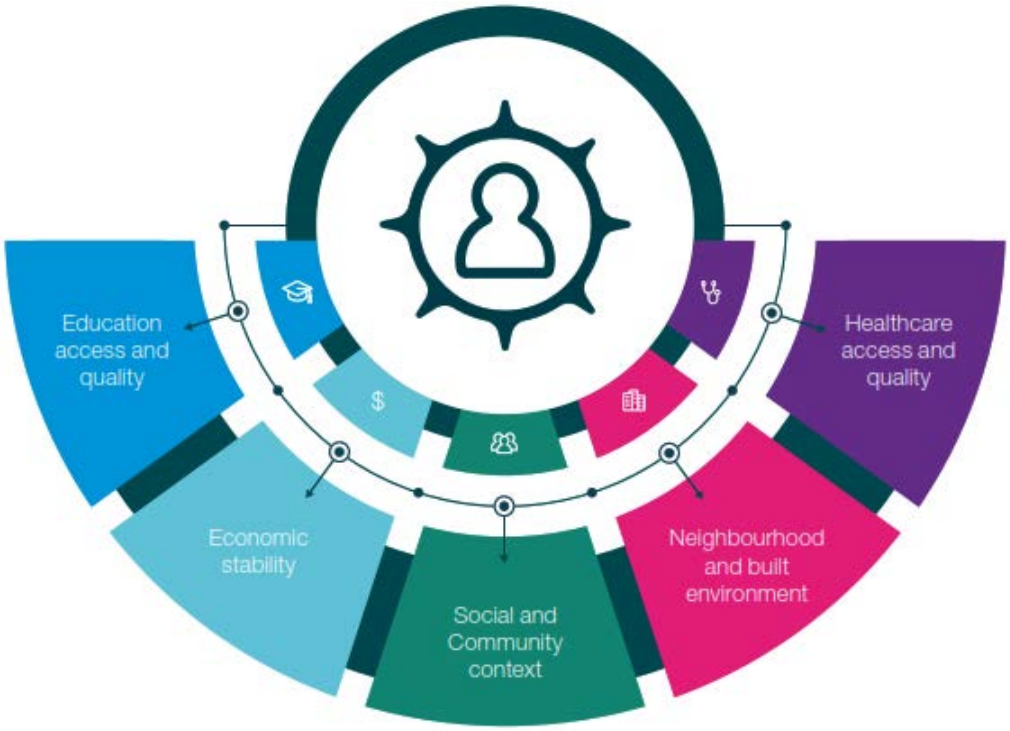
SDOH can play out in a number of ways that influence patient recruitment and retention and the practicality of participation. Access to health care can have an impact on access to trials, whether that means access to transportation, to the appropriate technology, or even to information about available trials. Another major consideration is the economic impact of clinical trial participation, as it may mean missing work or requiring childcare. By considering these determinants, trial sponsors can better navigate the barriers that might stand between certain groups of people and participation.

Building trust in the community

Related to social and community context, attitudes toward, and trust in, researchers have been identified as significant challenges in motivating underrepresented populations to participate in trials. If the group conducting clinical trials does not work to cultivate community relationships and treat participants with respect, feelings of exploitation and distrust can emerge. Indeed, a history of exploitation can play into some populations' views of clinical trials.

There have been instances in the past in which the medical field has been criticized for taking advantage of disenfranchised groups by conducting research without properly informing participants or gaining consent. Perhaps most famously, the USPHS Syphilis Study at Tuskegee Institute conducted a government medical experiment in the Tuskegee, Alabama, area that allowed hundreds of African American men with syphilis to go untreated so that scientists could study the effects of the disease.

A history of what may seem to some as inappropriate exclusion in research may have varying levels of influence over patient populations, depending on individuals and their culture. It may also lead to the researcher's conscious or unconscious bias, believing that certain minority patients will not participate due to anecdotal knowledge or that they are likely to early from the study. As a result, it is important for those conducting clinical trials to be aware of the historical context when they are building relationships with the relevant communities.



Social determinants can influence the practicality of clinical trial participation.

Building community relationships with a foundation of trust is a long-term process. When diverse participation goals are an afterthought, patient recruitment can be less successful. Establishing relationships with local influencers early and partnering with advocacy groups will support inclusion of diverse subgroups.

Identifying And Choosing The Right Sites For Diverse Subgroups

When identifying and choosing a trial site, its location and accessibility are crucial to recruiting and enrolling a diverse population. There can be a tendency to rely on established sites. However, these may not necessarily be accessible to diverse populations due to various factors such as location, lack of reliable transportation links, or patient mobility issues, which could ultimately limit their involvement.

A perception that FOHCs - which are primary care providers for those who have limited access to healthcare – lack experience and resources has made some researchers hesitant to involve them in clinical trials. Without their involvement, many qualified racial and ethnic minorities may continue to be excluded from clinical trials.

Particular subgroups also are challenged to access sites. One analysis published by the Alzheimer's Association found that the location of clinical trial sites conducting memory studies does not align cohesively with areas where adults over the age of 60 reside, putting excessive pressure on those sites that do align with the population and leaving many high-population zones without a trial site within 50 miles.[4]

Health Economics Aspect

One consideration that has previously impacted trial participants relates to insurance. For example, in the U.S., private insurers are required to provide reimbursement for participation in clinical trials. However, this previously was not the case for Medicaid, the federal- and state-run insurance program for people with low incomes.

However, in December of 2020, the U.S. Congress passed the Clinical Treatment Act, which requires Medicaid to cover routine care costs for patients with life-threatening conditions who are enrolled in clinical trials.[5] The act is expected to reduce health care disparities and level the playing field for millions of Medicaid recipients.

The NHS in the UK has recently set up an independent organization, Race and Health Observatory (NHSRHO), to identify and tackle health challenges facing people in Black, Asian and minority communities and examine health inequalities.

Conclusion

There are a multitude of compelling reasons for biopharmaceutical companies to embark on a journey to practice greater diversity and inclusion in clinical development as well as in their broader business strategies, including:

- The ability of sponsors and investigators to more accurately test the safety and efficacy of novel medical products in diverse populations where these medical products will be used
- An increased pool of individuals to be considered in clinical research
- The opportunity to address health disparities and to aim at equity
- Enhanced new perspectives and innovation by including diverse personnel

But above all giving access to the participants who can benefit most from the treatments makes sense if, as an industry, we are to be truly patient centric and improve patient lives.

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