



Failure to achieve diversity in pivotal clinical trials for conditions that impact diverse communities can mean acceptance of treatment principles in the absence of proper evidence to support them.

Clinical Trial Diversity, Drug Development, and Health Disparities

A Perspective from Project IMPACT

At any given time in America, there are thousands of clinical trials being conducted to evaluate the usefulness of therapeutic interventions. These clinical trials are widely recognized as an essential part of our ability to assure that the practice of medicine is truly evidence-based. It is also widely recognized that racial and ethnic minorities in the United States are significantly underrepresented in most clinical trials.¹ However, rarely is there open scientific discussion of underrepresentation in therapeutic trials and the consequential paucity of data from these populations as, perhaps, an important contributor to the health disparities that exist between so-called minority and majority U.S. populations.

Results of clinical trials for important therapeutic advances are enconced in medical literature, often without a thorough, public examination of diversity issues. Failure to achieve diversity in pivotal clinical trials for conditions that impact diverse communities can mean acceptance of treatment principles in the absence of proper evidence to support them. The goal of this review is to raise awareness of the issue of poor clinical trial diversity and the potential connection between issues of health disparities, and to raise awareness and engage the clinical research enterprise in efforts to address these issues.

About Project IMPACT

The National Medical Association (NMA) is a nonprofit organization and the oldest and largest medical organization representing the interests of African-American physicians. In 1999, NMA initiated Project IMPACT (Increase Minority Participation and Awareness of Clinical Trials), which responded to concern regarding inadequate representation of African-Americans and other minorities in clinical trials, including those sponsored by industry. The belief is that poor clinical trial representation contributes to a lack of knowledge applicable to medical interventions in this population. Although there are multiple contributors to this state of affairs, the ultimate result may be a perpetuation of existing U.S. health disparities.

Project IMPACT is a coordinated effort to raise awareness and educate physicians and consumers about research, and to develop physicians as effective clinical investigators and facilitators of research in minority communities. The project also aims to improve the validity of clinical trials data supporting the use of therapeutic interventions in diverse populations. Among many activities, IMPACT has sought to achieve its goals through educating physicians about clinical research, educating consumers about

the values and benefits of their participation in clinical trials, and facilitating physician involvement as investigators in the clinical research process.

Educating Consumers

In past years, it has been a commonly accepted precept that the primary reason for low African-American representation in clinical trials relates to mistrust of the process as a result of past abuses, such as the Tuskegee experiments (i.e., U.S. Public Health Services Study of Syphilis in the Negro Male).²

Although the existence of mistrust is well documented, the data do not support less willingness by minority patients to participate in clinical research when asked to do so.³ When mistrust of research is simply accepted by researchers without a serious effort to engage the minority patient in the discussion of the benefits of the research, it constitutes a continuing disservice to the patient and to the minority community. It essentially punishes the patient by perpetuating existing disparities through a continuing scarcity of applicable medical knowledge.

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Recognizing these issues, Project IMPACT has sought to educate the community regarding current research practices. Although mistrust exists in the community, the history of past research abuse is only partially to blame. We believe that significant contributors to mistrust of clinical research include lack of understanding of the process and its importance to the community, lack of access to culturally appropriate information, and lack of clinical researchers with longstanding relationships with these communities.

Project IMPACT has focused on use of culturally and linguistically appropriate communications with the community regarding the values and benefits of clinical research. Through health fairs, literature distributions, community presentations, and personal interactions, the project confronts questions regarding historical issues of research abuse, as well as the protections that have evolved to become a part of the current research environment. Consumers are given the tools they need to ask informed questions and make a personal assessment of whether a research opportunity is right for them.

Educating Physicians, Developing Investigators

The physicians practicing in the community will likely serve several roles. They will be caregivers, but may also be trusted advisers to their patients and respected members of the community. More often than not, minority community physicians share the culture and the racial and ethnic origins of the communities they serve. Additionally, these communities are often underdeveloped with respect to healthcare facilities, leading to a burden of larger patient populations with more severe needs. Thus, the responsibility associated with clinical research is commonly considered to be very challenging among those physicians who have an interest and are aware of

the need. Consequently, this population of patients is often totally disconnected from important research efforts absent advice and referrals from their physicians.

Project IMPACT recognizes that not all physicians will become clinical investigators. However, all physicians who provide care to patients are inevitably a part of the research process via their actions and subsequent patient observations. All physicians should be adequately educated about clinical research in order to advise their patients regarding appropriate research participation.

Diversity and the Clinical Research Enterprise

Under the 1994 National Institutes of Health (NIH) Revitalization Act, researchers who conduct clinical trials under sponsorship of the NIH are required to declare in a research plan their intent to recruit a population with appropriate gender and minority representation.⁴ The Food and Drug Administration (FDA) Modernization Act of 1997⁵, meanwhile, requires inclusion of women, and encourages inclusion and analysis of data from racial and ethnic minorities in industry-sponsored clinical trials of new medicines. However, FDA does not require minority representation or a stated plan to achieve an adequate level of representation consistent with the burden of disease in the population.

FDA guidance from 2005⁶ encourages industry sponsors to document racial and ethnic groups in clinical trials, but does not recommend levels of participation. We believe equitable population inclusion, as required by the NIH Revitalization Act, is consistent with the fundamental ethical principle of distributive justice as stated in the Belmont Report.⁷ Therefore, whether the financial sponsorship of a clinical trial is government or industry is irrelevant when considering the need to ensure that the benefits

as well as the burdens of research are appropriately distributed among the population with disease, as promulgated in the Belmont Report.

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The pharmaceutical and biotechnology research and manufacturing industries have been among the most prolific contributors to the improved quality of life and extension of lifespan that human beings have enjoyed over the past century. They have excelled at the practical application of knowledge for the betterment of human life, and have developed and marketed technology that has reduced hospitalizations, reduced the need for surgery in many illnesses, and prevented disease and disability for millions of people. Common diagnoses that disproportionately impact minority patients⁸, such as cardiovascular disease and stroke, several forms of cancer, diabetes, HIV/AIDS and multiple other infectious diseases, may have, in the past, been associated with an expectation of considerably shorter length and quality of life. However, we now consider many of these conditions as eminently treatable with medicines, often with little negative impact on the quality of life. Yet disparities in outcomes persist, often in the presence of equality of access,⁸ suggesting something may be missing in treatment.

Before any new pharmaceutical intervention can be made available for the treatment of human disease, it must be thoroughly evaluated in clinical trials. The clinical trials process includes administration to patients with the condition of interest with the objective of identifying the benefits relative to the risks. Well-designed and well-executed clinical trials are fundamental to the success of the industry; in fact, the industry is the world's largest sponsor of clinical trials.⁹ Data from industry trials support the regulatory approval, labeling, and marketing of new products, the formation of advertising claims relative to existing treatments, the projected economic impact of the treatment, and the basis for instructions on effective use and avoidance of potential unwanted effects.

An important measure of success in a clinical trial is, or should be, the applicability of the resulting data to the patient population who will use the product. Indeed, many aspects of American society lead to diversity of health and health outcomes from specific treatments.¹⁰ These include, but are not limited to, such intrinsic differences as genetically controlled receptor presence, function, density, and morphology; predisposition to or concurrent disease; body mass index; age; gender; and individual health experiences. In addition to intrinsic factors, there are extrinsic factors, such as variations in the environment (exposure to enzyme inducers and inhibitors), lifestyle, diet and nutritional habits, socioeconomic class, access to quality healthcare, cultural and personal beliefs about treatment and the healthcare system, and personal relationships with caregivers. Often, these factors will vary according to race and ethnicity in American society.

In the future, pharmacogenomic measures may obviate the need for some racial and ethnic assessment in clinical trials. At present, in order to ensure that we understand the risks and benefits of new therapeutic inter-

ventions, the clinical development program should include patients having the intrinsic and extrinsic diversity of the eventual consumers of the product.

The Changing U.S. Consumer

The American population is one of the most racially and ethnically diverse on earth, and arguably the largest market for new pharmaceutical products. This diversity continues to evolve at a rapid pace. Changes in the population bring with them changes in the incidence and prevalence of disease, and in the intrinsic and extrinsic factors that affect the outcome of treatment. Developers of innovative treatments must consider future changes in the population that are likely to occur over the course of a development cycle that can take a decade or more. Failure to do so raises the risk of developing and marketing products that are "out of touch" with the population of patients for which a treatment is intended.

Neither industry sponsors nor their regulators appear to act consistently upon knowledge of the potential for diverse response. Regulators approve labeling that provides little information regarding relevance of the population studied to the patient to whom the product may be administered.¹⁰ Products are often developed, approved, and promoted based on data that bear little resemblance to the diversity of the American population with the condition of interest.¹¹ This practice puts at

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risk our understanding of the benefits/risks and effective use of innovative treatments for the fastest growing segments of American society. Such limitations in our knowledge, while not thoroughly studied, have the potential to perpetuate disparities rather than eliminate them.

Absence of proof that these limitations have had a negative impact on the health of the minority population in the past must not be accepted as proof of absence of impact in the presence of persistent disparities in treatment outcomes. In this age where science has heightened consumer expectation for personalized medicine, medicine development must be consistent in addressing certain questions, such as: In whom does the medicine work? How can we make it safe and effective for the most people? Who should avoid the medicine entirely?

Industry invests substantial resources to obtain clinical trials data in the shortest time possible, since market exclusivity is directly compromised by development time. Frequently, speed is pursued through advertisement for clinical trial recruitment and repeated use of the same investigators. Speed is, probably, at least one reason for the growing use of non-U.S. investigational sites to expand the pool of patients to meet data demands. An industry concern may be that efforts to achieve interpretable clinical trial diversity may contribute to the cost and development time of new treatments and delay their availability to patients. Investing in the same pool of U.S. investigators with an expectation of achieving greater diversity may, in fact, cause program delays. However, the impact on speed from greater use of an expanded pool of qualified U.S. investigators with longstanding relationships with minority communities and less studied populations of patients has not been systematically explored. Anecdotal observations to date suggest that use of these sites may in fact speed the process. This is the subject of continuing study.

Are Institutional Review Boards Enablers?

Lest we consider clinical trial diversity to be only an issue of industry lacking a regulatory mandate, we must consider the role of institutional review boards (IRBs). IRBs are empowered to review human research to assure the equitable selection of participants¹² and to evaluate the research execution in the context of the Belmont Report. This role has largely evolved as one of excluding vulnerable, or “inappropriate,” populations from research. However, less attention has been given to responsibility for inclusion, that is, equitable distribution of the benefits and burdens of research to a racially and ethnically diverse population—one of the original bases for the Belmont Report. Thus, IRBs, by virtue of their charter to assure the ethical conduct of research, also have a role in facilitating the equitable application of research outcomes.

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A possible approach to fulfilling this objective would be a modified reapplication of the NIH requirements⁴ to industry-sponsored trials. Investigators would be required to provide a research diversity plan for protocol approval similar to that required for NIH-sponsored studies, but specific to the demographics of the local environment. The initial plan, along with recruitment data, would be subject to continuing review to assure that the trial population reflects the diversity of the population in the investigator's

community with the condition of interest.

Project IMPACT Experience to-Date¹³

For nearly a decade of Project IMPACT, tens of thousands of people across the country have received literature and participated in seminars and workshops on the general issue of clinical trial participation unassociated with any specific clinical trial. The impact of this training on the subsequent willingness of an individual to participate in a clinical trial is the subject of ongoing investigation. However, in all cases where programs have been conducted, the messages of research importance, values, benefits, and protections in the process have been well received.

Since its inception, Project IMPACT has provided various levels of training to more than 500 physicians across the U.S. The project maintains a database of physician investigators who have an interest in clinical research and have participated in a training course. Information from this database is made available to sponsors of clinical trials upon inquiry. Most of the physicians are associated with community practices of fewer than five physicians, and have little past experience in the conduct of clinical trials.

This latter fact represents a conundrum for the project. Sponsors most often use prior clinical trial experience as a prerequisite for involvement of a physician investigator, thus severely limiting the involvement of new minority physicians as investigators in clinical trials. Furthermore, physicians interested in becoming investigators are reluctant to do so because of concerns for being able to acquire and sustain study opportunities, as well as the potential of the investment to negatively impact their overall clinical practice viability. Therefore, the current challenge for Project IMPACT is to seek the support necessary to facilitate sustained involvement and eliminate

the barriers to achieving greater participation of these physicians and the patients who depend on them.

Conclusion

The future of clinical research demands a new paradigm of partnering with communities to understand their unique cultural issues and needs as a first step to establishing the trustworthiness of the research, as well as to recruit the researchers who are necessary to achieve successful outcomes. Realizing this paradigm represents an essential part of our ability to eliminate the current disparities of knowledge of the effective use of innovative technologies in diverse populations.

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