

Reflecting America's Patient Population— The Need for Diversity in Clinical Trials

By Katherine L. Kraschel, Associate Counsel, Yale New Haven Health System, New Haven, CT,
and William J. Roberts, Shipman & Goodwin LLP, Hartford, CT

African American men are twice as likely to die from prostate cancer as white men,¹ yet, they make up less than 5% of participants in prostate cancer clinical trials.² Statistics like this motivated a recent article in the journal *Cancer* that examines racial disparities in clinical trials and calls for action to improve minority participation.³ The article, funded by a National Institute on Minority Health and Health Disparities grant and the National Cancer Institute, has reinvigorated debates regarding and ethics of participant selection. The debate queries the existing regulatory framework and leads to considering regulations that might catalyze or compel changing the demographics of clinical trial participants to better reflect both the population at large, and the population most vulnerable to the condition or disease probed by the trial.

The History & Significance of Diversity in Clinical Trials

“Diversity” can be defined in a number of ways, but in the context of clinical trial participation, the focus has largely been race and gender. While the current discussion of clinical trials calls for greater inclusion of women and minorities, the development of bioethics and clinical trial regulation in the United States is largely borne of a history of past exploitation and abuse. As such, much of the regulatory focus has been on honoring individual autonomy to make an informed decision to opt out, rather than ensuring a just distribution of the benefits that accompany participation by creating an equal opportunity to opt in.

The first international agreement regarding standards of practice in human experimentation was the Nuremberg Code, enacted in 1948. The Code was a result of an American military tribunal that criminally charged German physicians who experimented on concentration camp prisoners during the Holocaust. It did not carry the force of law but made clear that participant consent was essential thus laying the groundwork for a regulatory scheme focused on patient autonomy to consent to participation.⁴

One of the most-cited examples of unethical biomedical research practices involved what has become known as the Tuskegee experiments in the United States. From 1932 to 1972, the U.S. Public Health Services monitored 600 African American men, 400 of whom were infected with syphilis, without informing participants of the disease or providing treatment (penicillin) when it became available in the 1950s. The stated goal of the study was to record the natural history of syphilis in hopes of justifying treatment programs for blacks.⁵ Some participants in the study died as a result.

Outside the context of experimentation, the off-label prescription of an unapproved drug—thalidomide—also would later shape regulatory policies. In the 1950s, thalidomide, a drug used as a sedative in Europe, and not approved by the Food and Drug Administration (FDA), was prescribed to pregnant women in the United States to control nausea and sleep. Only after thousands of women had taken the drug was it discovered that thalidomide causes severe deformities in the gestating fetus when taken by pregnant women. More than 12,000 babies were born with thalidomide-related deformities. It is against this backdrop that many landmark regulations were enacted.

On the heels of the Tuskegee experiments, the National Research Act was signed into law in 1974.⁶ The Act created the National Commission on the Protection of Human Subjects of Biomedical and Behavioral Research to articulate basic ethical principles to underlie the conduct of research involving human subjects. The Commission's work resulted in the Belmont Report, which was named after the location of intensive discussions in the Smithsonian Institution's Belmont Conference Center. The Report did not make specific recommendations but laid out the three principles that remain the widely accepted touchstones of the field of bioethics—autonomy, justice, and beneficence. These guiding principles have informed the regulatory scheme regarding human subjects research. Given the history of compulsory or involuntary experimentation, autonomy has played a prominent role in the regulatory framework by focusing on ensuring those who assume the risks involved in participation do so autonomously. Many of these concepts are familiar—informed consent, the FDA multiple-phase drug approval process, and monitoring by Institutional Review Boards (IRBs). At the same time, less effort has been devoted to ensuring justice by building an inclusive participant-selection system in which all who stand to benefit have access to participate.

Research has shown that differences in biology and genetics influence the efficacy of treatment.⁷ If a potential compound's performance is judged in a homogenous trial population, such results may not apply to the heterogeneous patient population. For example, only after it had been on the market for a number of years did the FDA approve a label change for zolpidem (the active ingredient in Ambien) upon determining that women metabolize the drug more slowly than men.⁸ It is a well-accepted principle that difference in genetic coding may make cancer treatment more toxic in one ethnic group than another, which only serves to reinforce the importance of diversity in clinical trials.⁹

Existing Regulatory Landscape

While legal interventions designed to preserve patient autonomy may be familiar terrain, the existing regulatory landscape on including women and minorities in clinical research is less so. Each of the major federal voices in regulating biomedical research has contributed to the discussion regarding participant selection. However, many of these efforts lack the teeth of enforcement, and data suggest the desired outcomes of such guidance or regulations remain aspirational.

The IRB guidebook speaks directly to the importance of including minorities: “The study design should provide for the adequate representation of women and minorities . . . so that the findings will be meaningful for those groups and they can, therefore, share in the benefits of the research. Adequate representation of women and minorities is particularly important in the studies of diseases, disorders, and conditions that disproportionately affect them.”¹⁰ By regulation, IRB approval requires “equitable” selection of subjects and advises that the IRB should be mindful of research involving vulnerable populations. It does not, however, contain any mandatory rules of *inclusion*.¹¹

The FDA issued guidelines in 1977 regarding inclusion of women in clinical studies.¹² These guidelines broadly excluded all women with child bearing potential as study participants—which effectively applied to all premenopausal women physiologically capable of becoming pregnant. The guidelines are a prime example of a reaction to a previous tragic incident (thalidomide), resulting in a regulation that sought to protect a “vulnerable” population and in doing so produced an approval process for drugs marketed to 100% of the population based upon evidence gathered from less than 50% of the population. In 1993, the FDA issued new guidelines specifically stating that excluding women with child bearing potential is not medically necessary because “the risk of fetal exposure can be minimized by patient behavior and laboratory testing . . .”¹³ The FDA also advised that “[t]he patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed.”¹⁴

More recently, 1998 FDA regulations require all New Drug Applications (NDAs) to document effectiveness and safety data for demographic subgroups including gender, age, and race, within the selected participants.¹⁵ There is no mandate, however, to include such subgroups in the study. In 2011, the FDA issued guidance outlining strategies for enrolling women in medical device trials.¹⁶ In 2012, the FDA Safety and Innovation Act required a report to Congress on diversity in clinical trials.¹⁷ The resulting report was published in August 2013 and included recommendations for the FDA to increase its focus on understanding how biological and genetic factors influence individuals’ reactions to a drug or device, and to work to ensure clinical trials adequately account for those factors.¹⁸ The report explicitly linked these recommended efforts to advances in personalized medicine. It should be emphasized, however, that the FDA only *requires* reporting on subgroups in NDAs, and does not impose an obligation to include any such subgroups in the research studies.

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Ahead of the FDA, the National Institutes of Health (NIH) issued guidelines in 1987 urging inclusion of women and minorities in clinical research.¹⁹ Subsequent regulations, promulgated pursuant to the NIH Revitalization Act of 1993, strengthened these guidelines by requiring a “clear and compelling rational and justification” for excluding women or minorities from any NIH-supported biomedical research.²⁰ The regulations require that if Phase I or Phase II trials indicate significant differences between subgroups, Phase III trial design must include at least two inquiries to investigate the differences identified.²¹

Most recently, the FDA released an action plan to (1) improve the completeness and quality of demographic subgroup data collection, reporting, and analysis; (2) identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation by demographic subgroups; and (3) make demographic subgroup data more available and transparent.²² The plan outlines the FDA’s short- and long-term objectives and proposed activities and includes plans to gather additional information on diversity in clinical trials and collaborate with other organizations to develop specific best practices and strategies to increase participation by demographic subgroups.²³

Other sources that may work to increase diversity in clinical trials include the FDA Office of Minority Health, which was established by the Affordable Care Act and has a mission of reducing ethnic and racial health disparities.²⁴ In addition, the Office of Women’s Health issued a 2011 report on strategies to engage women and minorities in clinical trials, and there has been some industry movement to increase the number of minority physicians conducting clinical trials in hopes of improving outreach and participation.²⁵ Finally, the organization Clinical Trials for Better Health is a collaboration between the Pharmaceutical Research and Manufacturers of America and the National Minority Quality Forum that works to raise awareness about the lack of diversity in clinical trials and to increase minority interest in participation.²⁶

Diversity in clinical trials is a multi-faceted problem with numerous causes, creating significant barriers to addressing the issue.

Efficacy of the Regulatory Landscape

It has been more than 20 years since the first government regulations and recommendations sought to increase diversity of clinical trials and to ensure that the proportion of minorities and women participants reflects the composition of the United States population at large. Despite the efforts described above, research indicates that racial minorities and women continue to be underrepresented in clinical trials, including those for pharmaceutical and device products that are marketed to treat or cure diagnoses that predominantly or disproportionately affect these groups.

With respect to race, evidence indicates that while whites account for 66.9% of the total U.S. population, they constitute 83.3% of clinical trial participants.²⁷ One example of this incongruous racial composition is the persistent lack of diversity in oncology trials. As of 2010, Americans who self-identify as white accounted for approximately 90% of the participants enrolled in oncology trials sponsored by the National Cancer Institutes.²⁸ This imbalance is found even in clinical trials that address cancer diagnoses that disproportionately affect non-white Americans, as illustrated by the percentage of African American men who participate in prostate cancer trials noted above.

Some evidence does suggest, however, more progress including female participants in clinical research—particularly in NIH-funded studies. According to a Government Accountability report, women achieved participation parity with men in NIH-funded research in 1997.²⁹ Similar progress was also noted for late-stage drug trials overseen by the FDA.³⁰ However, many trials that include women do not provide meaningful analysis of gender-related differences. Moreover, most trials operate outside of NIH-funding or FDA oversight, and the adequacy of female representation in clinical trials remains a concern.³¹ For example, females constituted only 33% of participants in recent clinical trials for cardiovascular devices.³² As such, additional efforts are needed to ensure adequate representation of females in clinical trials and adequate analysis of gender-related differences.

What Else Can Be Done?

The continuing lack of diversity in clinical research participation is a persistent problem. As discussed above, govern-

ment interventions have yielded unsatisfactory results. Diversity in clinical trials is a multi-faceted problem with numerous causes, creating significant barriers to addressing the issue. Below are some of the continuing challenges faced in attempting to improve diversity in clinical trials along with some proposals to address those challenges.

Increasing the number of racial minority and female participants in clinical trials may begin at the first step of the process—with the physicians who identify and recruit participants. Physicians should be educated about the importance of clinical trials to the health care system, the current lack of diversity in clinical trials, and the potential harms to patients resulting from this lack of diversity. Advocacy organizations, medical schools, and/or teaching hospitals with large research programs may be well positioned to provide such education.

While improved physician awareness is one important step, participant recruitment may nonetheless impair efforts to create a diverse trial pool. Evidence suggests that racial minority patients may be less likely to participate in a clinical trial if no racial minority investigators are involved,³³ potentially due to a lack of trust in the biomedical establishment following past exploitation of minority communities. This may be a significant barrier to minority participation given that non-whites are estimated to constitute less than 1% of principal investigators.³⁴

Increasing the number of minority principal investigators may improve the efficacy of outreach to minority patients. To this end, a collaboration between the Roswell Park Cancer Institute and the Eli Lilly Company aspires to increase minority participation by training minority physicians to serve as clinical investigators.³⁵

Transparent communication and education on the risks and benefits of participation, the importance of clinical trials for medical advancement, and the vital role patients perform in moving drugs and devices to market also should be part of any recruitment strategy. Recruitment tools should be reviewed and tested with non-white populations to assess their feasibility and cultural competency/relevance to a particular minority group. Different tools and messages may be appropriate for outreach to different groups or subgroups. For example, a recruitment strategy for a clinical trial testing the effectiveness of a pharmaceutical for treating a sexually transmitted disease may consider variances in how willing or open members of different groups may be when discussing a sensitive subject such as sexual activity.

Another set of challenges arises from disparities in access to the health care system. These challenges include ability to pay, location, transportation, and feasibility of participation. A patient needs to interact with the health care system in order to be recruited to enroll in a clinical trial, and often must have insurance coverage sufficient to pay for any costs related to such participation (as insurance may cover the non-experimental portions of the trial). While the Affordable Care Act may help reduce disparities in access and bring

more diverse populations into the health care system, many minorities and women may continue to lack interaction with the types of health care entities that conduct clinical trials or lack insurance coverage sufficient to enable recruitment and participation.

Transportation and proximity to trial sites may also be a barrier. The ZIP Code Analysis Project indicates that 80% of racial minorities reside in 20% of U.S. ZIP codes.³⁶ This means that, depending upon the trial site, potential minority participants may need to travel further than others to participate. Any lack of adequate public or private transportation options further complicates participation. Similarly, minorities and women may lack the flexibility necessary to participate in a trial, if participation requires including time off work or away from children under their care. To address these issues, recruitment efforts could be tailored to take into account geographic scope and any additional support and resources necessary to enable productive participation by minorities and women.

Cultural differences also can pose a barrier to more diverse participation in clinical trials. For example, in some instances, cultural differences regarding the value or validity of modern or Western medicine may mean that certain minority groups, such as Native Americans or Alaskan Indians, are unwilling or at least skeptical of participating in a clinical trial.³⁷ Attempting to bridge these differences should be done with care and cultural sensitivity in a way that respects other values and perspectives and helps ensure that the recruitment process facilitates, rather than hinders, participation.

Finally, increasing participation in clinical trials across all populations may require a shift in the culture of medical research to reconfigure traditional scientific frameworks and accept that initial studies in diverse groups may evolve into multiple studies exploring differences identified therein.

Looking Ahead

An increasingly diverse population requires medical products that are safe and effective across distinct subgroups. Looking ahead, we anticipate continued public and private sector efforts to educate physicians and patients, regulatory efforts to encourage (or require) consistent representation of diverse populations in clinical trials, and the consideration of effectiveness across population subgroups during the medical product approval process. As science advances and medicine moves towards more genetic and personalized interventions, equal access to clinical trials will only become a more pressing imperative, and the call for legal intervention to compel inclusive treatment development will only intensify. **C**

About the Authors



Katherine Kraschel (Katherine.Kraschel@YNHH.org) is Associate Counsel at Yale New Haven Health (YNHH). She is a member of the Legal and Risk Services Department's corporate services team. Ms. Kraschel also advises YNHH clients regarding research

compliance and serves on the Ethics Committee as well as one of the IRBs at Yale-New Haven Hospital.



William J. Roberts (WRoberts@goodwin.com) is an associate in Shipman & Goodwin LLP's health law practice group. Mr. Roberts represents hospitals, health care providers, and life science companies on a broad range of business and regulatory issues, including

corporate and regulatory compliance, fraud and abuse, data privacy, telemedicine, social media, government and internal investigations, and risk management issues.

Endnotes

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