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Encouraging Recruitment of Under-Represented Groups in Clinical Studies: A Sponsor's Perspective

Stephanie Stennett

Encouraging Recruitment of Under-Represented Groups in Clinical Studies: A Sponsor's Perspective

By

Stephanie Stennett

B.A., Chemistry
B.S., Biology
UNIVERSITY OF WEST GEORGIA

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I am thankful to my family and friends for continuing to encourage me to complete in this academic endeavor, and always reminding me of my future goals. I am also thankful to my committee for pushing me to think critically about this topic.

APPROVAL PAGE

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By

Stephanie Stennett, B.A., B.S.

Approved:

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Committee Chair

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Committee Member

_____

Committee Member

_____

Date

ABSTRACT

INTRODUCTION: Per the Belmont Report, which summarizes the ethical principles that guide human subject research, researchers must strive to equally distribute both the costs and benefits of human subjects' research among the population they serve. In the past, research studies disproportionally targeted convenient populations; participants were usually low-income and often minorities. Through a series of controversial and well known studies, protections were developed to better protect participants in research. However, these protections may have inadvertently caused a shift in the populations targeted for research. In recent history, women and minority groups have become under-represented in clinical research, particularly randomized controlled trials.

AIM: This capstone seeks to explore the implications of under-representation of certain groups in research and how industry (Sponsor and CROs) can better address this disparity to increase the participation of these groups in clinical studies.

METHODS: Current federal and international policies regarding human subjects' protections are documented and focuses on legislation in the United States that aims to increase the participation of women and minorities in research. The current costs and barriers to conducting a successful clinical trial, particularly as it pertains to recruitment of human subjects are explored. Using this information, the author proposes potential recommendations that could be incorporated at the industry level to successfully increase recruitment of under-represented groups in clinical trials.

DISCUSSION: Various strategies can be employed to encourage the participation of under-represented groups in clinical studies, including study design, site selection, use of community groups and recruitment firms to increase exposure and knowledge regarding clinical studies to the general population. Sponsors must also consider limitations that may affect recruitment, such as provider implicit bias. Incorporation of comprehensive recruitment strategies are vital to the improvement of under-represented groups in clinical studies.

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The Chair of the committee for this capstone is:

Professor's Name: Douglas Roblin, PhD

Department: Institute of Public Health

College: Health and Human Sciences

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Chapter I

BACKGROUND and LITERATURE REVIEW

1.1 Selected History of early Human Subjects Research

The history of human subjects' research is a storied, controversial narrative that spans centuries. Medical texts dating back to the 1500s highlight an accidental clinical trial in which Dr. Ambroise Pare, an army surgeon, discovered a novel way to treat soldiers wounded in battle. The standard of care at the time was to treat these wounds with boiling oil; however, during a particularly bloody period of battle, Dr. Pare's supply of oil was depleted and he resorted to treating his soldiers' wounds with a mix of egg yolk, rose oil and turpentine (Britannica, Ambroise Pare, 2007). The surgeon discovered that those soldiers treating with his turpentine mixture fared significantly greater than those treated with boiling oil alone (Bhatt, 2010).

The first planned controlled clinical trial did not occur until Dr. James Lind, a British naval surgeon, set out in to determine better treatments for sailors stricken by scurvy aboard the Salisbury. Dr. Lind was appalled by the alarming rate of mortality among his scurvy patients. In May 1747, he designed a study with all the essential elements of today's controlled clinical trial. He selected 12 scurvy patients with similar disease courses and restricted them to similar living quarters and diets for the short duration of the trial. Two sailors each were assigned to a total of 6 groups, similar to randomization arms. Dr. Lind published his results in a "Treatise on Scurvy" and during his trial discovered that the most immediate recovery occurred in sailors assigned to eat two oranges and a lemon per day along with their daily meals (Bhatt, 2010). Scurvy is now known to be caused by a several lack of vitamin C, but at the time of his study, Dr. Lind was hesitant to suggest including oranges and lemons in the daily diet of sailors due to the associated costs. The British Navy eventually incorporated the fruits into sailors' meals on Dr. Lind's recommendation, and this led to the eradication of scurvy among British sailors (Britannica, James Lind, 2007). These precursors to today's clinical trials proved to have a critical public health impact.

1.2 J. Marion Sims: dual face of American Medicine

Medical advances made in the 19th and 20th centuries reinforce the impression that risks of clinical research were often accepted by vulnerable, disadvantaged groups. Enslaved persons (and later the poor, captive and minority populations) were routinely used as human subjects as physicians and researchers endeavored to address pressing medical issues of the day. This literature review will briefly discuss selected watershed moments in the history of human subjects' research that have greatly influenced the development of federal and international regulations and which may illustrate the current barriers to recruitment of under-represented populations.

Widely regarded as the "founder of modern surgical gynecology", Dr. James Marion Sims is frequently discussed by researchers and bioethicists due to his early operations on enslaved persons (Wall, 2006). Dr. Sims performed many unsuccessful operations on enslaved children and adults hoping to address various conditions, but he eventually focused on a common but debilitating complication of childbirth: vesicovaginal fistula. This condition rendered women incontinent, virtually unable to participate in daily activities, and often alienated from society. Enslaved women were unusually afflicted by this condition due to a combination of factors, including malnutrition, the underdevelopment of their pelvises due to young maternal age, and the use of forceps during particularly difficult births (Washington, 2006). Since they were regarded as property, slaveholders were eager to have these women return to work. Dr. Sims eventually acquired several enslaved women with the condition in hopes to finally cure the condition. Over the next several years, the surgeon performed countless surgeries on these women without the administration of ether, which, at the time of his experimental surgeries, was a new form of anesthesia that could be used during operations. Once Dr. Sims perfected the procedure, he administered anesthesia to his white patients who underwent the same surgery. He also performed these surgeries without the formal consent of the enslaved women, as these women did not have the autonomy to object. Because of his contributions to the field of gynecology and the circumstances under which they were developed, Dr. Sims is hotly debated in discussions about the ethics of medical research. Washington notes that "Sims is an important figure in the

history of experimentation with African Americans because he so well embodies the dual face of American medicine to which racial health disparities owe so much." (Washington, 2006). The distribution of risks and benefits to participants in Dr. Sims' studies were not considered. Risks taken in his and other studies were most always borne by poor, disadvantaged populations while the positive results almost exclusively benefitted a society's privileged class.

1.3 Nazi doctors' experiments and the development of the Nuremberg Code

Some of the greatest known abuses of human subjects were committed under the guise of clinical experimentation conducted in Nazi Europe during the second World War. Nazi doctors carried out numerous types of experiments on Nazi concentration camp inmates, including testing methods of sterilization, vaccine trials, various types of transplants, and even methods of euthanasia, all in the name of German defense (Nelson, 2012). After the war, these doctors were put to trial in Nuremberg, Germany and ultimately found guilty of war crimes. A lasting effect of this trial has been the Nuremberg Code, which established the requirement of voluntary consent of human subjects for participation in research, and is the precursor to the development of the formal informed consent process. The tenets of the code have endured for more than 60 years and are included in Appendix A (Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, 1949).

1.4 Tuskegee Syphilis Study

The Tuskegee Study is well known in the history of human subjects' research in the United States. The fallout from the study ushered in a new era of human subjects' protections. Along with the results of other studies, abuses suffered under the Tuskegee Study influenced the development of the Belmont Report, a report summarizing guidelines for human subjects' research that is frequently referenced when discussing ethical oversight for human subjects' research.

In the early 1900s, the rate of syphilis among poor blacks in the southern United States had reached epidemic levels. Black men were disproportionately affected by the disease (Washington, 2006). At the time, there was no known effective cure for the condition (Washington, 2006). American physicians and researchers were also convinced of the racial dimorphism of the disease, most notably that in whites, syphilis targeted the nervous system almost exclusively, while in blacks, the cardiovascular system was the primary target (Thomas, 1991). The Rosenwald Fund established a medical program in Macon County, Alabama that offered treatment to county residents. However, the Great Depression bankrupted the financial resources needed to continue offering services to those seeking treatment.

The "Study of Syphilis in the Untreated Negro Male", more commonly known as the Tuskegee Syphilis Study was formally started in 1932 by the US Public Health Service. Under the guise of continuing treatment for affected black men, USPHS physicians established free clinics throughout Macon County, Alabama to recruit for a natural history study of the disease course of syphilis in untreated black males. Although more effective treatments were available at the time, the men enrolled into the study were treated with vitamins, 'ineffectual doses' of arsenic and mercury salve (Washington, 2006). The researchers did not want to alter the progressive disease course of the enrolled men in the study drastically, therefore the more effective treatment of Salvarsan was not offered to participating patients. Enrolled men and their families were convinced that they were receiving the best treatment available at the time. Advertisements used to recruit black men into the study stressed that they would be receiving treatment for their "bad blood", an ambiguous term used to describe several diseases that afflicted the community at the time (Thomas, 1991). Penicillin was proven to be an effective cure for syphilis in 1945; however, researchers kept the enrolled men treatment naïve and reassured their subjects that they were receiving the most effective treatment available at the time. The USPHS went so far as to circulate a list of enrolled subjects to area hospitals and clinics to request that providers not treat the men for syphilis and received draft waivers for subjects to prevent treatment (National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC, 2016). The study was formally stopped in 1972 amid public outcry regarding the study's ethical

failures. Eventually all affected men, their wives and children to whom they passed the disease were provided health and medical benefits as well as a formal apology from President Clinton on behalf of the United States.

1.5 Essential Documents pertaining to Human Subjects' Research

The abuses of research participants in the Nazi doctors' experiments and the Tuskegee Syphilis Study did not occur in a vacuum. Poor people and people of color, both often considered vulnerable populations, were routinely recruited into studies with questionable ethical and medical justification. Many advances in medical science were discovered on the backs (literally and figuratively) of prisoners (Hornblum, 1999). In response to several failures to protect human subjects in research, several seminal documents were drafted throughout the mid-20th century that are now considered the foundation of ethical oversight in human subjects' research. All current federal and international guidelines are, in part, a reflection of these documents. One such document is the Belmont Report, which is the result of a 4-day conference held at the Belmont Conference Center in February 1976 (Office of the Secretary, 1979).

Following the overwhelming condemnation of the Tuskegee Syphilis Study, the National Research Act was signed into law in 1974. This legislation created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and members of the Commission were from varying backgrounds, including academia, medicine, and civil rights organizations. The Commission was tasked with identifying ethical principles that would guide the conduct of human subjects' research along with clearly delineating the boundaries between clinical research and clinical practice (Office of the Secretary, 1979). After deliberating during the Belmont Conference, members of the Commission drafted the Belmont Report over the next three years. This document outlines "basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects" (Office of the Secretary, 1979). The three core ethical principles defined in the Report are respect of persons, beneficence and justice. These core principles have practical applications throughout research practice and

inform the appropriate informed consent process, assessment of clear risk-benefit criteria, and appropriate selection of human subjects for study participation.

The principle of respect for persons requires that researchers acknowledge the autonomy of a human subject involved in research, and, if that subject demonstrates diminished capacity, the principle requires protections are in place for that subject that will maintain his or her autonomy. This principle is practically applied through the informed consent process, which provides adequate information to a subject regarding the purpose of the study, study procedures, risks and benefits, and assurances that the subject is free to withdraw consent at any time. The process should be dynamic, allowing the potential subject to ask questions prior to enrollment and any time during their participation in the study (Office of the Secretary, 1979).

The principle of beneficence dictates that the researcher minimizes harm and maximizes the possible benefits for human subjects in research. The practical application of this principle requires a thorough assessment of benefits and risks associated with the study and that any potential risks are minimized or eliminated if possible. Benefits and risks must also be clearly communicated to potential participants during the informed consent process (Office of the Secretary, 1979).

The last principle of justice requires that the benefits and risks of research be distributed fairly and equally among the population. This principle is practically applied in the fair and moral selection of research subjects for a research study. Ethics committees (ECs) and institutional review boards (IRBs) are directly involved in the application of the core principles through their assessment of the informed consent process, study eligibility criteria, the target population of the study and the risks and benefits associated with the study (Office of the Secretary, 1979).

Chapter 2

Current Research Regulations and State of Clinical Study Enrollment

Sponsors, contract research organizations (CROs), and institutions implementing human subjects' research must adhere to a multitude of strict guidelines enforceable by federal and international agencies. These regulations and guidelines serve explicitly to protect subjects participating in research studies and encourage the collection of complete and accurate clinical data. The regulations encompass the informed consent process and elements (21 CFR Part 50); institutional review boards (IRBs) for study oversight (21 CFR 56); the responsibilities of the sponsor or its representative and the investigator (21 CFR Part 312 Subpart D); and other requirements needed to comply with federal law (Food and Drug Administration, 2016). If a study is being conducted in the US and OUS (outside of the United States), or if data from these studies will be used to submit applications to the regulatory bodies of other countries, sponsors and their representatives are also required to adhere to ICH-GCP guidelines and any country specific regulations. The International Conference on Harmonization's Good Clinical Practice guidelines are international standards that countries generally incorporate into their individual regulations. While it is formally considered a unified standard for studies conducted in the European Union, Japan and the United States, many other countries have in some way incorporated its minimum standards, and in many cases, have enacted stricter regulations (International Conference on Harmonization, 2015).

These regulations and guidelines have certainly improved the protection of human subjects, particularly vulnerable populations. However, an unintended consequence of strict guidelines on the conduct of human subjects' research is a shift in the populations recruited to participate in clinical studies. Researchers have almost always recruited from a population of convenience. Prior to the implementation of regulations related to consent, those populations of convenience often included vulnerable populations that could not effectively advocate for themselves and autonomously choose whether a research study was in their best interest. In the current research climate, a population of convenience may include a doctor's private patients and regular seekers of care within the US healthcare system. Principal investigators often carry a patient

load or recruit from established private practices, clinics or hospitals, and because of this, they are likely to recruit patients from a higher socioeconomic class, which often correlates with medical insurance status (Williams, 2004). Uninsured patients are less likely to enroll in studies than insured patients for several reasons, including confusion on what portion of clinical care is covered when participating in clinical studies, lack of exposure to clinical study information and limited access to clinical studies based on geographic location (Williams, 2004). Other barriers to participation for minority populations may include geographic location of study centers, transportation, difficulty in finding childcare, and the complexity of the clinical trial (Wendler, 2006). While these barriers may affect all potential subjects, they are particularly restrictive to the participation of minority subjects.

Overall patient participation in human subjects' studies remains very low across the nation, no matter the patient's ethnic background. For example, in cancer clinical trials, approximately 3% of adult cancer patients participate in clinical trials per the Institute of Medicine's Forum on Drug Discovery, Development and Translation (Institute of Medicine, 2010). It is difficult to accurately gauge the participation rates of under-represented groups in clinical studies overall based on the lack of publicly reported demographic data. The FDA's Center for Drug Evaluation and Research reviewed subgroup demographic data for 45 novel drugs approved in 2015. The participation rate among minorities is disproportionately lower than Caucasians. Of the 45 novel drug applications reviewed, CDER noted that that approximately 5% of the subjects were African American and 12 % of the subjects were Asian American across therapeutic areas (FDA Center for Drug Evaluation and Research, 2017). Participation by gender is also disproportionate in certain therapeutic areas. For example, in an NIH-funded analysis of clinical trials for vascular disease, researchers noted that while women constituted 21.5% of all aortic aneurysm repair (AAR) surgeries from 2004 to 2005, they represented just 9.0% of participants in surgical trials conducted for AAR (Hoel, 2009). Other estimates compiled by the Society for Women's Health Research and the FDA's Office of Women's Health show that approximately 1% of clinical trial participants are Hispanic, which is far less than their

total representation in the overall US population (Society for Women's Health Research and Office of Women's Health (FDA), 2011).

Lack of patient participation creates a huge financial loss to pharmaceutical, medical device and biotechnology companies. Patient recruitment and retention accounts for about 40% (approximately $1.89 billion in 2011) of the total annual budget dedicated to clinical trials by US pharmaceutical and biotechnology companies (Nuttall, 2012). Delayed completion of patient enrollment drives up overall study costs and delays investigational product development and regulatory body submission approval. Nuttall observed that almost 80% of all clinical trials conducted in the US do not finish on time, and many are delayed by 6 months or more (Nuttall, 2012). Lack of patient participation in clinical trials is also quickly becoming a public health concern as improved treatment options cannot get to market without positive results on safety and effectiveness from extensive clinical trials. Furthermore, it is difficult to generalize study results to the overall patient population if a study does not recruit a diverse, representative sample of subjects. These concerns are forcing the pharmaceutical and biotechnology industries to quickly develop innovative strategies on improving the process of investigational product development, including the recruitment and retention of a representative sample of clinical study subjects.

Chapter 3

Recommendations

3.1 FDA Safety and Innovation Act: Section 907

Repeated analyses and studies have demonstrated that limited study results for subgroups makes generalizability of clinical trial results difficult (Adams-Campbell L. e., 2004). Though this assertion is well known, implementing effective strategies to increase participation of under-represented demographic groups has been challenging. The National Institutes of Health and the Food and Drug Administration have attempted to address these challenges through various laws passed by Congress, such as the NIH Revitalization Act of 1993 and the recent FDA Safety and Innovation Act of 2012, Section 907. Though the NIH Revitalization Act ambitiously set out to increase the inclusion of women and minorities in medical research, disparities have persisted for over 20 years since the law's implementation (goBalto, 2016).

The FDA's Safety and Innovation Act of 2012 is a comprehensive law that addresses several aspects of the agency's regulatory authority. Section 907 specifically addresses "reporting of inclusion of demographic subgroups in clinical trials and data analysis in applications for drugs, biologics, and devices" (Food and Drug Administration, 2012). The full text of the FDASIA Section 907 is included in Appendix B. While regulations require that sponsors submit demographic subgroup data, the FDA did report that the data collected did not necessarily allow for meaningful analysis by subgroup or were the populations sufficient in allowing for detection of differences among the subgroups analyzed (Food and Drug Administration, 2014).

The FDA developed a detailed action plan to further support study sponsors in their approach to subgroup enrollment and data analysis. The FDASIA action plan has 3 priorities outlined in Section 907 that aim to address the following:

Quality: to improve the completeness and quality of demographic subgroup data;

Participation: to identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation;

Transparency: to improve the public availability of demographic subgroup data.

Studies conducted or funded by the National Institutes of Health are required to structure their protocols in such a manner that addresses appropriate recruitment of subgroups. This action plan is a valuable blueprint that can be used by all industry sponsors to ensure improved recruitment of subgroups that will allow for generalizability of study data to the general population. Sponsors must work to incorporate the following recommendations to increase demographic subgroup recruitment.

3.2 Subgroup demographic data collection

To assess the current state of subgroup recruitment, sponsors must collect and report detailed race and ethnicity demographic information on current and future clinical studies conducted both within and outside of the United States. This information includes age, sex, race and ethnicity demographic data. In this context, ethnicity is defined as "Hispanic or Latino" or "Not Hispanic or Latino" (Food and Drug Administration, 2014). Clinical studies conducted by or funded by sponsors may vary greatly in the terms used to define the demographic data collected (Ma, 2007) and what demographic data is reported with study results (Corbie-Smith, 2003). This detailed information is needed to accurately quantify the under-representation of demographic subgroups in clinical studies. As noted in sections 1.2 and 1.4 of the action plan, this type of data collection is necessary to accurately determine the subgroups recruited into clinical studies.

3.3 Study Design

Sponsors and Contract Research Organizations (CROs) develop protocols to adhere to strict federal and international regulations. For clinical trials to meet requirements for FDA investigational device and drug approval, sponsors must be able to demonstrate overall safety and effectiveness of the proposed investigational product while also proving non-inferiority to current approved treatments. Creating

comprehensive enrollment criteria also allows sponsors to account for sources of bias in trial results and to appropriately apply statistical analysis (Patsopoulos, 2011). However, these criteria may unnecessarily exclude patients based on their age, laboratory results, existing comorbidities, concomitant medications, and medical history. Site investigators often site restrictive eligibility criteria as a difficulty in meeting recruitment goals for clinical trials (Nuttall, 2012). Certain subgroups are disproportionately burdened by a variety of chronic conditions, and eliminating these potential patients based on these comorbidities may limit the ability of sponsors to enroll this population (Adams-Campbell, 2004). Some exclusions are certainly needed to protect the safety of patients; however, some exclusions, particularly those that address chronic comorbidities, may eliminate subgroups that may have otherwise been appropriate candidates.

Researchers at Howard University's Cancer Center conducted a study that tracked newly diagnosed cancer patients between January 1, 2001 and December 31, 2002 to assess their eligibility and participation in clinical trials at the site (Adams-Campbell, 2004). This study showed that restrictive eligibility criteria and the lack of available studies at the site resulted in eligibility of only 8.5% of the 235 patients followed during the study (Adams-Campbell, 2004). The study authors noted: "The inclusion and exclusion criteria, as well as a lack of available clinical trials opened at our institution, were the primary barriers for African American participation at Howard University Cancer Center." (Adams-Campbell, 2004)

An overly restrictive set of enrollment criteria may also reduce the real-world application of a therapy due to the homogenous sample population enrolled in the study. Study results may indicate a positive average treatment effect for the therapy but not account for the heterogeneity in treatment effect, defined as the "nonrandom variability in the direction or magnitude of a treatment effect" (Varadhan, 2013). In fact, it is possible to observe adverse effects in certain subgroups of a treatment population despite a positive average treatment effect for the study overall (Kent, Rothwell, PA, & Altman, 2010). Because of inevitable differences between subgroups and even individuals within a subgroup, it is more appropriate for sponsors to consider a heterogeneity in treatment effect analysis, which will capture variations within a patient

population. These types of analyses can be defined in the statistical plan, which defines how study data will be analyzed and can address the minimum number of subjects needed overall and in each subgroup to effectively complete the subgroup analysis. Protocols must be designed with study endpoints in mind, which will vary based on the therapeutic area and phase of the study. Section 2.2 of the FDASIA action plan urges sponsors to critically consider their enrollment criteria during protocol development to ensure that demographic subgroups are not unnecessarily excluded from participation in the clinical study.

Sponsors may look to aspects of the pragmatic trial design as a potential basis for protocol design when designing trials aimed at demonstrating efficacy in the general patient population. Pragmatic trial design aims to confirm whether the intervention in question is truly applicable to routine clinical practice (Patsopoulos, 2011). Phase IV trials often employ this type of design, but this design may be more broadly applicable within clinical studies. Pragmatic trials have high external validity and are implemented in diverse settings, which allows for greater representation of the patient population (Patsopoulos, 2011). Pragmatic trials also better demonstrate the heterogeneity in treatment effect as the sample size must be sufficiently large enough to account for variations across a patient population.

3.4 Site Selection and Site Specific Recruitment Plans

Recruitment plans vary greatly among sponsors and CROs. While sponsors will develop metrics to track progress of recruitment overall, they may hesitate to develop specific recruitment strategies tailored to individual sites or subgroups. Some sites and IRBs may limit the types of advertisements that can be used at their site. Sponsors may not feel equipped to develop specific recruitment measures by site because of geographic differences and may rely solely on sites to develop a plan for their study's recruitment efforts. This may especially limit recruitment of under-represented populations because recruitment strategies that may effectively attract a certain demographic may work poorly in others. Some private practices and clinics may also rely heavily on their normal patient population for study recruitment, and this population may be somewhat homogenous depending on the geographic location of the site. Sponsors can address these issues

by diversifying their site selection. They may use some strategies defined within the community-based participatory research approach to broaden their reach for recruitment. They may also employ a recruitment specialist or firm to develop specific recruitment strategies with sites once they are identified and selected. Section 2.3 of the FDASIA action plan addresses broadening diverse participation in clinical research, and looks to document successful strategies for subgroup recruitment.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is an example of successful minority recruitment. The randomized, multi-center trial was sponsored by the National Heart, Lung, and Blood Institute of the NIH and enrolled a total of 10,251 patients in sites across the US and Canada (Kingry, 2007). Patients were randomized to one of three complementary treatment strategies aimed at reducing rates of major cardiovascular morbidity and mortality in patients with diabetes (Kingry, 2007). It was particularly successful in recruiting minority patients because one of the study recruitment goals was to recruit at least 33% minority participants into the study and recruitment plans were developed to meet this goal (Kingry, 2007). The study was divided into two recruitment phases: the vanguard phase and the main trial. National study organizers used the vanguard phase assess overall study feasibility and to document successful recruitment strategies for the study's target population. The ACCORD trial incorporated a comprehensive recruitment strategy that involved national, regional and local level coordination in recruitment and site management (Kingry, 2007). At the national level, study directors maintained a Recruitment and Retention Subcommittee that issued a Recruitment and Adherence Survival kit to all participating sites, and on the local level, sites were encouraged to maintain at least three active recruitment strategies at all times (Kingry, 2007). Based on their comprehensive, proactive approach to recruitment, the ACCORD trial met their recruitment goals for the vanguard phase of the study early and met their overall recruitment goal within 3 months of their targeted date.

3.4.1 Established research sites

Sponsors and CROs often target investigators that they have worked with on past studies. These investigators will have the required clinical trial experience, are familiar with the patient population needed for trials, and may have been successful in meeting recruitment goals in past studies. However, continuing to use the same investigators for multiple trials may limit the diversity of patients recruited depending on the geographic location of the site. To overcome this limitation, sponsors can work with investigators to identify the groups in the geographic area that have been historically under-represented in clinical studies. This can improve recruitment of under-represented subgroups at sites with existing sponsor relationships.

There are several strategies that can be employed to do this, including use of social media and traditional media outlets such as radio and newspapers for advertisements. Sponsors can create culturally diverse advertisements that can be used by existing sites to reach a new population of patients. It is important to provide culturally and linguistically diverse advertisements and study materials to investigators to recruit from populations that may not speak English as a first language (Symonds, K, Mitchell, & Raghavan, 2012). Sponsors can be proactive in providing these translated templates to sites such as informed consent templates and recruitment documents. It would be helpful to employ research staff that can effectively communicate culturally and linguistically diverse populations as this can also encourage participation in clinical studies. Time is one of the most critical resources in a clinical trial; therefore, is important that sponsors to have these translated templates early in the site approach process to facilitate timely IRB approval.

3.4.2 Geographic location

Clinical trials are often conducted at locations in suburban areas, and potential minority subjects frequently note that trial visit location can limit their ability to participate (Williams, 2004). Sponsors may benefit from exploring new potential sites in diverse geographic locations, both in population size and make-up. This may increase accessibility for potential research participants, as convenience of site location is often

cited as a consideration for enrollment by potential subjects (Nuttall, 2012). Sponsors should review the demographics surrounding potential new clinical sites to determine if the population that site serves will provide a diverse patient population for enrollment. Sponsors may look to partner with the medical schools of Historically Black Colleges and Universities (HBCUs) and affiliated teaching hospitals, medical offices and clinics to recruit more diverse populations. As mentioned earlier in this chapter, some potentially eligible cancer patients at Howard University Cancer Center were unable to enroll in clinical trials due to a lack of available trials at this center (Adams-Campbell, 2004). Approaching these types of institutions may increase the potential patients from under-represented populations that are able to enroll.

The ACCORD trial successfully demonstrated the benefit of using geographically diverse sites that covered rural, suburban and urban areas. The study was coordinated at the national level by the National Heart, Lung and Blood Institute, and used seven clinical center networks across the US and Canada to manage regional coordination of the study's 77 clinical sites (Kingry, 2007). Individual sites used various recruitment strategies to reach all parts of their surrounding geographic area (Kingry, 2007). The ACCORD trial is one example of how geographically diverse clinical sites can improve recruitment of clinical trials.

3.4.3 Community Groups and Community-Based Participatory Research

Community based participatory research (CBPR) is a concept that has been successfully implemented for the conduct of several types of research studies and health promotion programs. This type of research approach is used often in studies sponsored by the National Institutes of Health and would be greatly beneficial for sponsors to employ for recruitment of under-represented populations into their research studies. The CBPR approach establishes community input and participation in the development, implementation and conduct of a community based health program (Corbie-Smith G. e., 2003). This type of input has proven quite successful in engaging the community and developing excitement and commitment to the implementation of a research study. However, this type of approach requires significant

investment on behalf of the sponsor to create authentic and long-lasting community ties (Corbie-Smith G. e., 2003).

For example, the NIH-funded 'Kick It at Swope' project evaluated the use of bupropion for smoking cessation in African Americans in Kansas City, Missouri (Harris, Ahluwalia, & al., 2003). Researchers used both proactive and reactive recruitment strategies to engage potential participants in the community. This included dissemination of study information to lay persons in the community and in-person recruitment of potential subjects at area clinics and community centers (Harris, 2003). Researchers also approached churches and other community organizations to gain buy-in from trusted leaders in the community.

CBPR has also been used in Latino communities with the use of *promotoras de salud*, which are trained health workers recruited from the lay community to implement health programs (Koshkan & Friedman, 2013). As mentioned earlier, this type of approach requires significant sponsor investment of finances, time and resources to truly establish authentic ties in the community that can be used for current and future studies. These types of investments can include engagement of faith-based and community organizations to establish a presence in the community and build trust with potential participants, and establishing relationships with area institutions that may serve as a source of potential patients. Financially, sponsors will also have to fund translation of study and recruitment materials appropriate to their target population, and may need to address transportation barriers to clinical trial locations by providing reimbursement for transportation for potential patients (Morgenlander, 2009). This type of investment in the community can be used long-term to continue to recruit under-represented populations into clinical trials.

3.4.4 Recruitment Specialists: A growing field

Sponsors are increasingly turning to recruitment specialists to address recruitment challenges. These specialists may be employees of a sponsor or part of a separate company that solely focuses on site-specific recruitment plans that can be implemented upon IRB approval. Recruitment specialists can be valuable

throughout all phases of protocol development and implementation. They can provide input to the sponsor on prospective protocol design to assess aspects of the study that adversely affect recruitment, particularly recruitment of subgroups. One of the biggest barriers to subgroup recruitment into clinical studies in awareness of available trials (Wendler, 2006). Specialists can be utilized to complete targeted assessments of the demographics surrounding a potential study site on the sponsor's behalf to determine if the required patient demographic mix could possibly be recruited from this area. They can also create a comprehensive recruitment plan that will best market the study to a diverse population, including the appropriate translated documents to target linguistically diverse populations. As noted previously, these documents should be available at the beginning of the study, prior to patient recruitment, so as to not unnecessarily delay the submission of any regulatory documents.

Data is limited as to the effect and success of these recruitment specialist as the patient recruitment services industry is in its early development (Industry Standard Research, 2014). However, with the increase of sponsors employing this type of specialist to target recruitment, evidence may develop that supports the use of this type of specialist. Several CROs now have dedicated recruitment groups that will address recruitment issues based on demographic area and type of study protocol (Industry Standard Research, 2014). In recent years, several companies have also emerged that exclusively address recruitment issues and can be hired by the sponsor to work directly with selected sites on recruitment goals.

Chapter 4

Discussion

Disparities in research participation of vulnerable populations parallel the poorer health outcomes in these subgroups. Health disparities exist across almost every medical condition, and some vulnerable populations have greater associated morbidity and mortality (Meyer, 2013). The limited inclusion of subgroups in clinical studies limits the generalizability of study results to the populations treated in the general population (Hughson, 2016).

While scientists have readily accepted differences in treatment response by gender, some hesitate to accept that significant differences exist between population subgroups due to external factors such as healthcare access (Hussain-Gambles, Atkin, & Leese, 2004). Studies have shown that responses to treatment can differ based on demographic subgroup (Hughson, 2016). In response to variation in physiological response to prescribed treatment, the American Heart Association developed new ethnicity-specific formulas to predict the risk of development of atherosclerosis based on evidence supporting differences in effects between Caucasians and African Americans (Goff, 2014). It is important to design recruitment protocols into clinical trials that will account for the heterogeneity in treatment response that may exist between ethnic subgroups.

The socio-ecological model (SEM) can be used as a framework to analyze the various barriers to recruitment and participation in clinical studies for under-represented groups. The intrapersonal level is comprised of an individual's personal knowledge and belief system that may potential influence their choice to participate in research (Salihu, 2015). Potential participants have indicated concerns about loss of confidentiality, perceived financial costs of participation, and concerns about medical treatment within a clinical study as reasons for declining participation (Symonds, 2012). Other factors that have been identified as deterrents to minority patient participation are mistrust of medical providers based on past interactions, and skepticism regarding the purpose of a research study (Harris, 2003). These barriers may be addressed

through thorough explanation of a clinical study's purpose, procedures and risks and benefits within a documented informed consent process (Salihu, 2015).

The interpersonal level of the SEM can be used to identify barriers that may be generated from a potential participant's social network, which includes medical providers and study investigators (Salihu, 2015). The issue of implicit provider bias, which is well documented in clinical practice (Blair, 2013), may deter recruitment of subgroup populations who might benefit from participation in clinical studies. Some providers think minority participants have limited understanding of the complexities of clinical trial protocols and may consider these participants less compliant with research protocols (Williams, 2004). Physicians may incorrectly assume that these patients will not agree to participation in a clinical trial due to perceived mistrust of providers (Wendler, 2006). Providers may also be unaware of available clinical studies seeking referrals or may hesitate to refer patients to clinical studies if they are unsure of the study's objectives and procedures (Williams, 2004). To combat this, sponsors and CROs may see a benefit in officering cultural competency training to research staff specifically aimed at understanding what factors may discourage subgroups from participating in research and to address possible provider bias. Sponsors may also train investigators on effective strategies for communicating study goals in a succinct manner to potential referring providers. An increase in minority investigators may also lead to an increase in recruitment of minority participants in research (Valcarcel & Diaz, 2006). In the interim, sponsors can encourage the cultural competency of research investigators and staff to better connect with the minority populations they seek to enroll.

Barriers at the institutional and community levels of the SEM may also exist that hinder minority recruitment and participation in clinical trials. The institutional level includes organizational level policies and structures that can deter both the conduct of a clinical study and the recruitment of minority participants into a clinical trial (Salihu, 2015). Some barriers at this level include limited facility resources for the conduct of clinical trials and lack of patient navigation systems that can connect potential minority

participants with available clinical trials (Symonds, 2012). The community level includes barriers that can affect entire communities such as lack of transportation to study site locations and an overall disconnection of the medical provider community with minority subgroups that may benefit from research (Symonds, 2012). Community-wide attitudes of mistrust may also hinder minority recruitment at this level, and may require community outreach by medical providers and sponsors to address this mistrust.

To dynamically assess study recruitment into clinical studies, sponsors may incorporate the use of NIH Inclusion Enrollment Report and the CONSORT Flow diagram into their tracking of study progress. The Inclusion Enrollment Report is a tool that collects basic demographic data on study enrollment efforts and is required at the inception and conclusion of an NIH-funded research study (U.S. Department of Health and Human Services, 2016). It is currently required for annual reports of NIH-funded studies, but it can be used to track any gaps in enrollment of demographic subgroups throughout the conduct of a study. This type of data can be used to adjust study timelines as needed to address recruitment of under-represented subgroups. The CONSORT Flow diagram was developed by the CONSORT group, and the diagram can be used to show trends in recruitment and to identify potential obstacles to recruitment and enrollment based on study design (Schulz KF, 2010). Both tools can be used by sponsors in tandem to regularly track recruitment efforts and to adjust recruitment strategies throughout the conduct of study, allowing for appropriate recruitment of under-represented groups into their studies.

As research becomes more globalized, sponsors must design clinical trials that can be implemented in the US and at international sites. Regulations on human subjects' research vary by country and can be more stringent than US regulations. In addition, any data collected from international sites and used for FDA investigational applications must adhere to US federal regulations. As pharmaceutical, medical device, and biotechnology companies strive to globalize their products, they must address protocol design and recruitment strategies that will encompass both the US and international regulations and that will recruit diverse populations that will be truly representative of the patient populations they intend to treat.

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THE NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

["Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.]

APPENDIX B: Statutory Language, Section 907 of FDASIA

SEC. 907. REPORTING OF INCLUSION OF DEMOGRAPHIC SUBGROUPS IN CLINICAL TRIALS AND DATA ANALYSIS IN APPLICATIONS FOR DRUGS, BIOLOGICS, AND DEVICES.
(a) REPORT.—

(1) IN GENERAL.—Not later than 1 year after the date of enactment of this Act, the Secretary, acting through the Commissioner, shall publish on the Internet web site of the Food and Drug Administration a report, consistent with the regulations of the Food and Drug Administration pertaining to the protection of sponsors' confidential commercial information as of the date of enactment of this Act, addressing the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity, is included in applications submitted to the Food and Drug Administration, and shall provide such publication to Congress.

(2) CONTENTS OF REPORT.—The report described in paragraph (1) shall contain the following:
(A) A description of existing tools to ensure that data to support demographic analyses are submitted in applications for drugs, biological products, and devices, and that these analyses are conducted by applicants consistent with applicable Food and Drug Administration requirements and Guidance for Industry. The report shall address how the Food and Drug Administration makes available information about differences in safety and effectiveness of medical products according to demographic subgroups, such as sex, age, racial, and ethnic subgroups, to health care providers, researchers, and patients.
(B) An analysis of the extent to which demographic data subset analyses on sex, age, race and ethnicity is presented in applications for new drug applications for new molecular entities under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), in biologics license applications under section 351 of the Public Health Service Act (42 U.S.C. 262), and in premarket approval applications under section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e) for products approved or licensed by the Food and Drug Administration, consistent with applicable requirements and Guidance for Industry, and consistent with the regulations of the Food and Drug Administration pertaining to the protection of sponsors' confidential commercial information as of the date of enactment of this Act.
(C) An analysis of the extent to which demographic subgroups, including sex, age, racial, and ethnic subgroups, are represented in clinical studies to support applications for approved or licensed new molecular entities, biological products, and devices.
(D) An analysis of the extent to which a summary of product safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity is readily available to the public in a timely manner by means of the product labeling or the Food and Drug Administration's Internet web site.

(b) ACTION PLAN.—
(1) IN GENERAL.—Not later than 1 year after the publication of the report described in subsection (a), the Secretary, acting through the Commissioner, shall publish an action plan on the Internet web site of the Food and Drug Administration, and provide such publication to Congress.

(2) CONTENT OF ACTION PLAN.—The plan described in paragraph
(1) shall include—
(A) recommendations, as appropriate, to improve the completeness and quality of analyses of data on demographic subgroups in summaries of product safety and effectiveness data and in labeling;
(B) recommendations, as appropriate, on the inclusion of such data, or the lack of availability of such data in labeling;
(C) recommendations, as appropriate, to otherwise improve the public availability of such data to patients, health care providers, and researchers; and
(D) a determination with respect to each recommendation identified in subparagraphs (A) through (C) that distinguishes between product types referenced in subsection (a)(2)(B) insofar as the applicability of each such recommendation to each type of product.

[Food and Drug Administration. (2014). FDA Action Plan to Enhance the Collection and Availability of Demographic (E) Subgroup Data. FDA Report, Washington DC.}

FDA Action Plan at a Glance

The action plan reflects FDA's commitment to encourage the inclusion of a diverse patient population with regard to sex, age, race and ethnicity in biomedical research used in marketing applications for FDA-regulated medical products.

	Priority One: Quality—improving the completeness and quality of demographic subgroup data	**Actions**	**Time frame**
1.1	***Reviewing and developing a work-plan for updating, and/or finalizing, relevant guidance on demographic subgroup data, including FDA staff training and outreach to external stakeholders, as needed, for implementation***	-CBER and CDER plan to review, update, and/or finalize, as needed, relevant industry guidance and internal FDA good review practice documents to encourage greater demographic subgroup representation in clinical trials, subgroup analysis and communication of results. -FDA plans to incorporate recommendations from the Evaluation of Sex-Specific Data guidance into reviewer templates, to provide staff training and develop and offer an external webinar on use of the guidance. -FDA plans to begin drafting a guidance document on analysis and reporting of ethnicity, race, and age in medical device clinical studies.	*Short-term and intermediate-term completion goal*
1.2	***Working with sponsors to revise medical product applications to enhance information on demographic subgroups in medical product applications***	-CDER and CBER plan to revise the guidance on the Integrated Summary of Effectiveness sections of NDAs and BLAs.	*Intermediate-term completion goal*
1.3	***Strengthening FDA reviewer training by adding education/training around demographic inclusion, analysis and communication of clinical data***	-FDA plans to require training for new clinical trial reviewers on the importance of demographic subgroup data inclusion, analysis, and communication. -FDA plans to offer additional education and training courses for experienced reviewers and other staff to better clarify FDA's data collection and analysis expectations related to demographic subgroups.	*Intermediate-term completion goal*
1.4	***Enhancing FDA's systems for collecting, analyzing and communicating diverse clinical information to optimize safe and***	-FDA plans to work, to the extent possible, towards better standardization of data collection categories for age, racial and	*Intermediate-term to long-*

	effective use of medical products in diverse populations over the total product life cycle	ethnic groups in submitted applications to facilitate harmonized data collection and analysis of subgroup outcome trends. -FDA plans to revise MedWatch forms to enable a standardized collection of demographic information on possible adverse events that occur after medical products are broadly available on the U.S. market. -FDA plans to strengthen systems and infrastructure for making better use of data once products are broadly available on the U.S. market.	*term completion goal*
1.5	***Conducting research on specific areas of public health concern related to demographic subgroups***	-Office of Women's Health (OWH) plans to develop a new women's health research roadmap that will help to better coordinate research across the agency and target OWH funding to projects that answer specific regulatory research questions and emerging priorities from the product review centers. -Office of Minority Health (OMH) plans to develop research projects leading to better understanding of medical product clinical outcomes in racial/ethnic demographic subgroups. -OMH plans to collaborate with NIH's National Human Genome Research Institute in research into the role of genetics and genomics in health disparities. -As resources allow, FDA plans to develop a program of directed research in which FDA investigators could select a certain disease category and conduct an in-depth look at the data contained in relevant applications submitted over a specified time period (i.e., 5 to 10 years).	*Intermediate-term completion goal*
	<u>Priority Two:</u> Participation—identifying barriers to subgroup enrollment in clinical trials and employing strategies to encourage greater participation	**Actions**	**Time frame**
2.1	***Seeking further clarity about barriers to subgroup participation rates***	-OMH plans to convene a meeting of experts in 2015 to better understand contemporary barriers to participation of minorities in clinical trials.	*Short-term completion goal*

2.2	***Implementing efforts to enhance appropriate use of enrollment criteria in clinical trial protocols***	-FDA plans to work with industry to try to ensure appropriate use of enrollment criteria in clinical trial protocols.	*Short-term completion goal*
2.3	***Collaborating with NIH, industry and other interested stakeholders to broaden diverse participation in clinical research***	-FDA plans to establish a joint working group with the National Institutes of Health Inclusion Policy Officer to establish a framework of collaboration and information exchange on inclusion policies, practices and challenges. -OWH plans to collaborate with NIH Office of Research on Women's Health on a national campaign to educate and promote the importance of clinical trial participation, focusing on women. -FDA plans to work with industry to develop and share best practices related to recruiting a broad representation of patients for clinical research supporting FDA medical product applications.	*Short-term and Intermediate-term completion goal*
2.4	***Using FDA's communication channels to encourage clinical trial participation by demographic subgroups***	-FDA plans to explore various ways to communicate to demographic subgroups about clinical trial participation. -FDA plans to issue an FDA Consumer Update on clinical trial participation by demographic subgroups and distribute it in both English and Spanish versions to FDA's subscriber list (approximately 140,000 subscribers) and to our targeted media list.	*Short-term completion goal*
	<u>Priority Three:</u> Transparency—making demographic subgroup data more available and transparent	**Actions**	**Time frame**
3.1	***Posting demographic composition and analysis by subgroup in pivotal clinical studies for FDA-approved medical products***	-CDER and CBER plan to post demographic information from pivotal clinical studies for newly-approved medical products such as New Molecular Entities and Biologics License Applications. -FDA plans to explore approaches for public user-friendly ways of posting demographic information from medical device pivotal studies and completed post-approval and postmarket surveillance studies.	*Short-term and Intermediate-term completion goal*

3.2	***Identifying potential methods to consistently communicate information on demographic subgroups in medical product labeling***	-FDA intends to work with industry, advocacy groups, risk communicators (including FDA's Risk Communication Advisory Committee), and other stakeholders to explore potential methods for communicating meaningful information on demographic analyses to the public. -CDRH plans to conduct a study with health care professionals to improve usability and understanding of medical device labeling and product instructions for use.	*Intermediate-term completion goal*
3.3	***Implementing communication strategies that are sensitive to the language and health literacy needs of underrepresented populations***	-FDA plans to implement communication strategies that are sensitive to the needs of underrepresented subpopulations, with a focus on language access and health literacy.	*Short-term and Intermediate-term completion goal*
3.4	***Establishing an internal FDA steering committee to oversee and track implementation of the action plan***	-FDA plans to establish an agency-wide steering committee to oversee implementation of the action plan. -FDA envisions that the Steering Committee will begin planning for a public workshop to be held within 18 months of the publication of the action plan.	*Short-term completion goal*

[Food and Drug Administration. (2014). FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data. FDA Report, Washington DC.]