Clinical Research – A Journey Toward Diversity

Clinical trials are an essential part of the drug development process. Regulatory agencies such as the Food and Drug Administration (FDA) use information gathered from clinical trials to decide if medicines are safe and effective. It is important to have ethnic diversity in clinical trials to better understand diseases, and the full impact of certain drugs. Different ethnicities can have unique responses to the same disease. Studies have shown that MS can be especially active in African Americans. The effectiveness of many drugs can also vary depending on the patient’s ethnicity, lifestyle, culture and genetic makeup. For example, about 50 percent of Asian patients and 75 percent of Pacific Islanders lack the enzymes required to activate Plavix (a blood thinner). Certain classes of hypertension drugs have recently been found to be less effective in African American patients.

According to the National Institutes of Health (NIH), minorities account for fewer than 10 percent of patients enrolled in clinical trials. African American men are twice as likely as Caucasian men to die from prostate cancer, yet they represent just 4 percent of prostate cancer clinical trial participants. Suicide is one of the top three causes of death among
Asian American women under 45 years of age, yet they represent just 1 percent of major depressive disorder clinical trial participants. And while the prevalence of diabetes among Mexican Americans and Puerto Ricans is more than double that of Caucasians, those groups combined represent just 4 percent of diabetes trial participants. Many research findings cannot be applied to minorities because they are not represented in the clinical trial data that has been collected.

One primary reason for low participation rates in clinical trials among minorities is a lack of trust among potential participants. This mistrust is based on a long history of unethical clinical research. This, and a general lack of trust in health care institutions or the health care system in general, have negatively affected the participation of minorities in research.

The Tuskegee Syphilis Study is probably the worst case of unethical human subjects research in the history of the United States. This was a research project conducted by the U.S. Public Health Service. Six hundred low-income African-American men, 400 of whom were infected with syphilis, were monitored for 40 years. Free medical examinations were given; however, subjects were not told about their disease. Researchers withheld treatment even when penicillin became widely available. Researchers did not tell the subjects that they were in an experiment. Many died of the disease, infected their wives, and/or passed congenital syphilis to their children. The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare. President Clinton apologized to study subjects and their families in 1997, however residual mistrust of clinical trials remains today among many members of the African-American community.

German physicians conducted medical experiments on thousands of concentration camp prisoners without their consent during World War II. Most of the subjects in these experiments died or were permanently crippled as a result. After the war, some of those responsible for these atrocities were brought to trial. These trials; held in Nuremberg, Germany, led to the formulation of the Nuremberg Code in 1948. The Nuremberg Code was the first international document stating that subjects should give consent for participating in research and that the benefits of research must outweigh the risks.
In the late 1950s, thalidomide was approved as a sedative in Europe. It was not, however, approved by the Food & Drug Administration (FDA) in the United States. Thalidomide was prescribed to control sleep and nausea throughout pregnancy, but it was soon found that taking this drug during pregnancy caused severe deformities in the fetus. Many patients did not know they were taking a drug that was not approved for use by the FDA, nor did they give informed consent. Some 12,000 babies were born with severe deformities due to thalidomide. This disaster led to the adoption of the Kefauver Amendments to the Food Drug and Cosmetic Act, requiring drug manufacturers to prove to the FDA the effectiveness of their products before marketing them.

In the 1960’s, hepatitis experiments were carried out on mentally disabled children at the Willowbrook State School in Staten Island, N.Y. These experiments were approved by the New York Department of Health. Researchers intentionally infected subjects with hepatitis and observed its natural progression. The investigators maintained that hepatitis infection was inevitable for this population. However, only children whose parents gave permission to participate in the studies were admitted to Willowbrook. The consent process for this study was unethical in light of this coercive admission policy.

Henrietta Lacks was a poor, African-American mother of five who died in 1951 of cervical cancer. Before Lacks died, a research team at Johns Hopkins University in Baltimore took a sample of tissue from her cervix. Researchers found that they were able to grow these cells in dishes, which fueled a cell line called HeLa cells. This was a major breakthrough that gave researchers a powerful new tool against disease that has since generated billions of dollars. The first benefits from HeLa cells were in their use in developing the first vaccine against polio. More than 60,000 articles have been published based on the use of HeLa cells, including cancer and AIDS research. There has been much controversy over the fact that Lacks never agreed that these cells could be used for research. For years, her own family had no idea that her cells were still alive in petri dishes in scientists' labs. Scientists collected the family’s blood to map HeLa genes without proper informed consent after they learned of the cell line’s existence. Despite this, the Lacks family remains supportive of research that has been done and recently endorsed restricted access to HeLa genome data. Under an agreement with the National Institutes of Health, Lack's genome data is accessible only to those who apply for and are
two representatives of the Lacks family now serve on the NIH group responsible for reviewing biomedical researchers’ applications for controlled access to HeLa cells. Additionally, any researcher who uses that data is asked to include an acknowledgement to the Lacks family in their publications.

The Declaration of Helsinki was developed by the World Medical Association in 1964. This is a set of ethical principles for clinical research that is the basis for Good Clinical Practices used today. The Declaration of Helsinki states that informed consent from research participants is necessary, and that the risks of research should not exceed its benefits. According to this Declaration, research should be conducted by medically and scientifically qualified individuals, and be based on the results from laboratory and animal experimentation. Finally, the Declaration of Helsinki states that research protocols should be reviewed by an independent committee prior to initiation. As a result, all research involving human subjects in the U.S. must be reviewed and approved by an ethics committee, or an Institutional Review Board (IRB).

The National Research Act was approved by Congress in 1974, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of clinical research involving human subjects and to develop guidelines to be followed when conducting such research. The Commission drafted the Belmont Report, which established three basic ethical principals in clinical research: respect for persons, beneficence, and justice. Respect for persons dictates that individuals participating in research must be given the opportunity to choose what happens to them and those that are less capable are entitled to protection. This is the foundation for the informed consent process that is currently used in clinical research. The consent form must include sufficient information for potential subjects to understand the procedures, benefits and risks of a given study, and to make a voluntary choice to participate. Beneficence is the principal that clinical research should maximize possible benefits and minimize possible harms so that human subjects are not harmed. Justice requires that the selection of research subjects be done in a manner that distributes the
benefits and risks of research fairly. These three ethical principals are the cornerstones for regulations involving human subjects today.

The Common Rule was adopted in 1991 as the federal policy regarding human subject protection. The Common Rule is the baseline standard of ethics to which any government funded research in the United States is held. Nearly all academic institutions in the US hold their researchers to these statements of rights, regardless of funding. The Common Rule includes requirements for researchers obtaining and documenting informed consent; and requirements for IRB membership, review of research and record keeping. The Common Rule also includes additional protections for certain vulnerable research subjects (pregnant women, prisoners and children), and requirements for assuring compliance by research institutions.

The current regulations, which have been in place since 1991, were developed at a time when research was conducted predominantly at universities and medical institutions, and each study generally took place at a single site. Since then, research with human participants has grown in scale and become more diverse and data has become digital. In 2017, the U.S. Department of Health and Human Services (DHHS) and 15 other federal agencies issued a Final Rule to update the regulations, which allows more flexibility in keeping with today’s dynamic research environment. The new rule strengthens protections for people who volunteer to participate in research. For example, it includes a requirement for consent forms to provide potential research subjects with a better understanding of a project’s scope (including its risks and benefits), so they can make a more fully informed decision about whether to participate. The Final Rule also includes a requirement that consent forms for some federally funded clinical trials be posted on a public website. The Final Rule also ensures that the oversight system does not add inappropriate administrative burdens, particularly to low risk research. For example, it includes requirements to use a single IRB for multi-institutional research studies, eliminates continuing review for some minimal risk research, and establishes new exempt categories of research based on the level of risk they pose to participants. In addition, the Final Rule includes behavioral health studies in the definition of clinical trials. Researchers using stored identifiable data or biospecimens for their studies will have the option of relying on broad consent obtained for future research. Pending review of the current administration, the effective date for all changes except cooperative research (projects involving more than
one institution) is January 2018. Changes to cooperative research requirements will be effective in January 2020.

The Code of Federal Regulations includes rules for the protection of human subjects in studies involving any test article subject to FDA regulation (i.e. drugs, devices, food/color additives). 21 CFR Part 50 includes regulations for informed consent, and additional safeguards for children in these studies. 21 CFR Part 56 includes regulations regarding Institutional Review Boards. In addition, the NIH and Office for Human Rights Protection (OHRP) have required all people conducting or overseeing human subjects research to have training in research ethics since 1999.

The federal regulation of clinical research has made great strides from a dark past to protect the rights of those that volunteer to participate in clinical research. Additional work must continue that couples these assurances with effective recruitment methods to ensure that minority and vulnerable populations are reached and engaged in meaningful and respectful ways. Improving diversity in clinical trials is essential to providing medical products that are safe and effective for everyone.

In October 2016 the Accelerated Cure Project was approved for a Eugene Washington PCORI Engagement Award by the Patient-Centered Outcomes Research Institute to support the development of the Multiple Sclerosis (MS) Minority Research Engagement Partnership Network. This network, developed in partnership with Feinstein Kean Healthcare, is designed to identify disparities and increase participation by minorities in MS medical research.