Milestones in the History of Human Subjects Protection

Nuremberg Code (1947): Ten Elements of the Nuremberg Code
   1. Voluntary consent of subjects
   2. Anticipation of scientific benefits
   3. Benefits outweigh risks
   4. Animal experiments need to be conducted first
   5. Suffering is to be avoided
   6. No intentional outcome of the research should be death or disability
   7. Protect the subject from harm
   8. Subject is free to stop participation at any time
   9. Investigators need to be qualified
  10. Investigator will stop if harm occurs

The Declaration of Helsinki
Initially adopted by the World Medical Association in 1964 and subsequently modified every couple of years; it is a landmark international agreement on making additional safety recommendations to the Nuremberg Code. It said we should do preliminary experiments on animals prior to recruiting humans. It pointed out that we shouldn't enroll a human in a study unless the importance is in proportion to the risk. It also recommended formation of safety committees that later on became data safety monitoring boards (DSMB) and Institutional Review Boards (IRB).

Beecher Article
In 1966, Dr. Henry K. Beecher was an anesthesiologist who wrote an article in the NEJM describing 22 examples of unethical research conducted and published by "reputable" researchers of the time. He wrote, "medicine is sound, and most progress is soundly attained," however, if unethical research is not prohibited it will "do great harm to medicine." At that time it was assumed that the only unethical research was that which went on in the Nazis' prison camps.

Research on Obedience to Authority
At Yale University in the early 1960s, Stanley Milgram was a social psychologist who devised a series of experiments to examine the circumstances under which naïve individuals would follow instructions whose consequence was the apparent injury of another person. Publication of the research, and a dramatic film of the study, generated much controversy among psychologists. Some argued that subjects had been harmed, if not through the stress of the experiment itself, then through the "inflicted insight" into their own personalities. Nevertheless, the relevance of the research to what was current events of the day, the trial of Adolph Eichman, who maintained that he was just following orders as he signed papers condemning concentration camp victims to death, made the findings all the more compelling.

The Jewish Chronic Disease Hospital Study
In 1963, studies were undertaken in Brooklyn, NY, at the Jewish Chronic Disease Hospital, which is now called Interfaith Hospital of Brooklyn. The doctors then did a terrible "study" on unwitting, unsuspecting,
unconsenting patients on the body’s ability to reject cancer cells. They injected live cancer cells intravenously into patients and watched to see if they developed any signs of neoplasia. They then proudly published their results for the world to read.

**The Willowbrook Study**
In the early 1960s, unethical research was conducted at the Willowbrook State School in Staten Island, NY, on vulnerable mentally retarded children to better understand the natural history of the hepatitis virus. Most of the kids "caught" the highly infectious virus after they came there. The doctors then decided to "coerce" the parents into enrolling their children in an experimental study whereby their children were deliberately infected with the live hepatitis virus. Only parents who agreed to the research were able to get their ‘retarded’ children into Willowbrook. This controversial case raised important questions about the adequacy and freedom of consent, inadequate disclosure of the child’s risk of later developing chronic liver disease, and the lack of information given to parents about access of doses of gamma-globulin.

**Tea Room Study**
In the 1960s, there was a study on the homosexual practices in public restrooms, then, to contact the men at a later time to conduct further investigation on their behavior. The researcher went undercover and gained the confidence of the gay men. He identified 100 active participants by tracing their car license numbers. A year after he completed the initial study, he distributed a "social health survey" throughout the communities where he knew the participants lived. The ethical problems were: use of a vulnerable population, reinforced the image that social scientists use deception casually in research, and lack of proper informed consent.

**Tuskegee Syphilis Study**
The study was conducted by the United States Public Health Service back in 1932 and involved poor blacks in rural Alabama who were enrolled in an observational study of the natural history of untreated syphilis. The men were recruited without informed consent and, in fact, were misinformed that some of the procedures in the interests of research (spinal taps were explained as back shots) were actually "special" free treatments. By 1936 it had already become apparent that many more infected men than controls had developed complications. In the 1940s penicillin was determined to be efficacious for syphilis. This study ended in 1972 when a reporter exposed the horrors of the study. President Clinton issued a formal apology a few years ago to the families of the over 400 black men with syphilis and the 200 men without syphilis who served as health controls who were victims of the prolonged and knowing violations of the rights of a vulnerable group of research participants.

**National Research Act: 1974**
The Act established the National Commission for protection of Human Subjects of Biomedical and Behavioral Research, codified DHHS Policies as 45 CFR Part 46 Subpart A, and legislated formation of IRBs.

**The Belmont Report**
Released in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavior Research, it provided more strenuous protection to human research subject volunteers. It was entitled *Ethical Principles and Guidelines for Research Involving Human Subjects.* The Belmont Report
pointed out the differences between "practicing medicine on patients" and "performing medical research on human research subject volunteers." It cautioned researchers to think about what hat they were wearing at any particular time. It identified three basic principles to guide researchers to provide safer medical research:

**Respect for persons** is the principle involving recognition of the personal dignity and autonomy of individuals and the need for special protection to be afforded to those with diminished autonomy. That is, the person has to understand what they're getting into. Autonomy is protected by the consent process. Each prospective subject must be given ample time and information to decide whether to participate or not in a research study. There is need not only for initial consent, but also for an ongoing and continual informed consent process as the study progresses.

- Obtain Informed Consent
- Respect the privacy of research subjects
- Does the consent process and protocol maximize autonomy?
- Additional protections put in place to safeguard vulnerable populations
- The study needs to maximally protect subject privacy
- Need to adequately inform subjects of potential risks

**Beneficence** or the lack of malficence has to do with not doing harm and maximizing benefits. Explaining the risks, benefits and alternative treatment options available. This principle is the basis for the risk/benefit ratio assessment in which principal investigators, sponsors, CROs, IRBs and Independent Ethics Committees (IEC) and institutions all seek to ensure that any risks are minimized, and not taken unless there is likely to be a benefit to the individual research subject volunteer.

- Use the best possible research design to maximize benefits and minimize harms
- Make sure the researchers are able to perform the procedures and handle the risks
- Research without a favorable risk/benefit analysis may not be conducted
- Looking to see if adequate research designs can be improved further
- Identifying and minimizing risks
- Identifying and maximizing benefits

**Justice** has to do with how researchers distribute the burdens of research and who actually receives the benefits. For example, do you include only poor people in a study that would only have benefit to rich people? Therefore, the principle of distributive justice requires that both the burdens and the benefits of research be distributed equitably. Subject selection should be based on those who stand to bear the risks should also be the ones who will benefit from the research.

- Select subjects equitable: recruitment targets the population that will benefit from the research
- Avoid exploitation of a vulnerable population or a population of convenience
- Does the recruitment unfairly target a population?
- Are the inclusion/exclusion criteria fair?
- Autonomy/respect to decide whether to participate or withdraw from a study

**Havasupai Case**

In 1990, Arizona State University researchers collected blood samples from the Havasupai tribe originally for diabetes research. Later determined (through publications) that blood samples were used in research on schizophrenia and inbreeding, as well as student studies which supported the migration hypotheses of the peopling of North America via the Bering Strait land bridge (in contradiction to their own origin stories). Tribal plaintiffs said they never would have allowed the blood to be collected had they known it would be used in such ways. Case has helped amplify general mistrust between Native
Americans and the scientific community. Settlement (2010) contains several provisions, but ASU must pay plaintiffs $700M, return all blood samples in its possession, and return documents like lab books, genealogy materials containing research derived from the samples, and IRBs at universities in the suit cannot approve ongoing or new research involving the samples, plus provide a list to the tribe of entities to which it previously transferred the samples. Brings about questions of consent and how subjects can be truly “informed” about future uses:

- Are tiered consents realistically feasible?
- How should IRBs evaluate which method of consent should be required?
- Should investigators be required to provide evidence of community consultation?

Leads to questions about what subject attitudes toward biobanking research – like what should be in the consent?

Death of a Normal Volunteer
On March 31, 1996, a 19-year-old female Asian-American student at the University of Rochester responded to an advertisement for study patients to undergo bronchoscopy for the harvest of alveolar macrophages. The patient died of an overdose of lidocaine. The protocol didn't limit the dose. The pulmonologist didn't record the amount of lidocaine administered.

Death on Gene Therapy Trial
In the fall of 1999, 18-year-old Jesse Gelsinger died as a result of his participation in a gene therapy trial. Jesse had a rare metabolic disorder, ornithine transcarbamylase deficiency syndrome (OTC), which was being controlled with diet and medication. Researchers were testing an innovative technique using adenovirus gene therapy. Shortly after treatment Jesse experienced multiple organ failure and subsequently died. This case catapulted research with human subjects into the national media. Serious concerns related to conflict of interest, data safety monitoring, and informed consent have made the Gelsinger case the most contemporary illustration of continued doubts about the ethical integrity of research with human subjects. This case has instigated deliberations on all these controversial topics at the national level.

Veterans Administration
In April 1999, all research projects at the Veterans Administration West Los Angeles Medical Center were shut down after many allegations of medical research performed on patients who did not consent. An investigation showed that not only was research being done on patients without who had not given informed consent, but also that research was being done on patients who had expressly refused consent.

Duke University Medical Center
On May 12, 1999, the federal government ordered Duke Clinical Research Institute to stop its research due to problems with its IRB. The order was issued by the US Department of Health and Human Services' Office for Protection from Research Risks (OPRR).

The Office of Human Research Protections
The Office of Human Research Protections (OHRP) was established in 2000 with the US Department of Health and Human Services to increase the focus on protecting human research participants. Former name: Office for Protection from Research Risks (OPRR).
Death of a Healthy Research Subject Volunteer

Ellen Roche was a 24-year-old healthy research volunteer enrolled in an experimental drug study at Johns Hopkins Medical Center who died on June 2, 2001, following her participation in an asthma research study where she inhaled hexamethonium. *The New York Times* reported she died because of failure of scientists and administrators to recognize that the experiment was unsafe. All research there was halted until the following actions were taken to strengthen research oversight:

- Increasing the number of IRBs
- Intensifying training for all IRB members
- Web-based instruction using IRB 101 by Public Responsibility in Medicine and Research (PRIM&R)
- Academic review of protocols prior to IRB submission to evaluate study design, safety and validity
- Working with OHRP
- Establish a committee to review and revise policies for participation of students/employees in research
- Taken steps to ensure timely, written documentation of IRB deliberations
- Re-review consent forms: purpose, risk, benefits
- Collaborate with a pharmacist and a librarian for literature searches on potential side effects
- Query FDA to see if IND is necessary
- Need to notify IRB if change in protocol or SAE
- Pharmacist to be involved in the preparation of study drugs
- Random quality control checks to insure safety and adherence to best practices