NYU Langone Medical Center

“Either a necessary evil or an unbearable hindrance”*

How the community and IRB can work together

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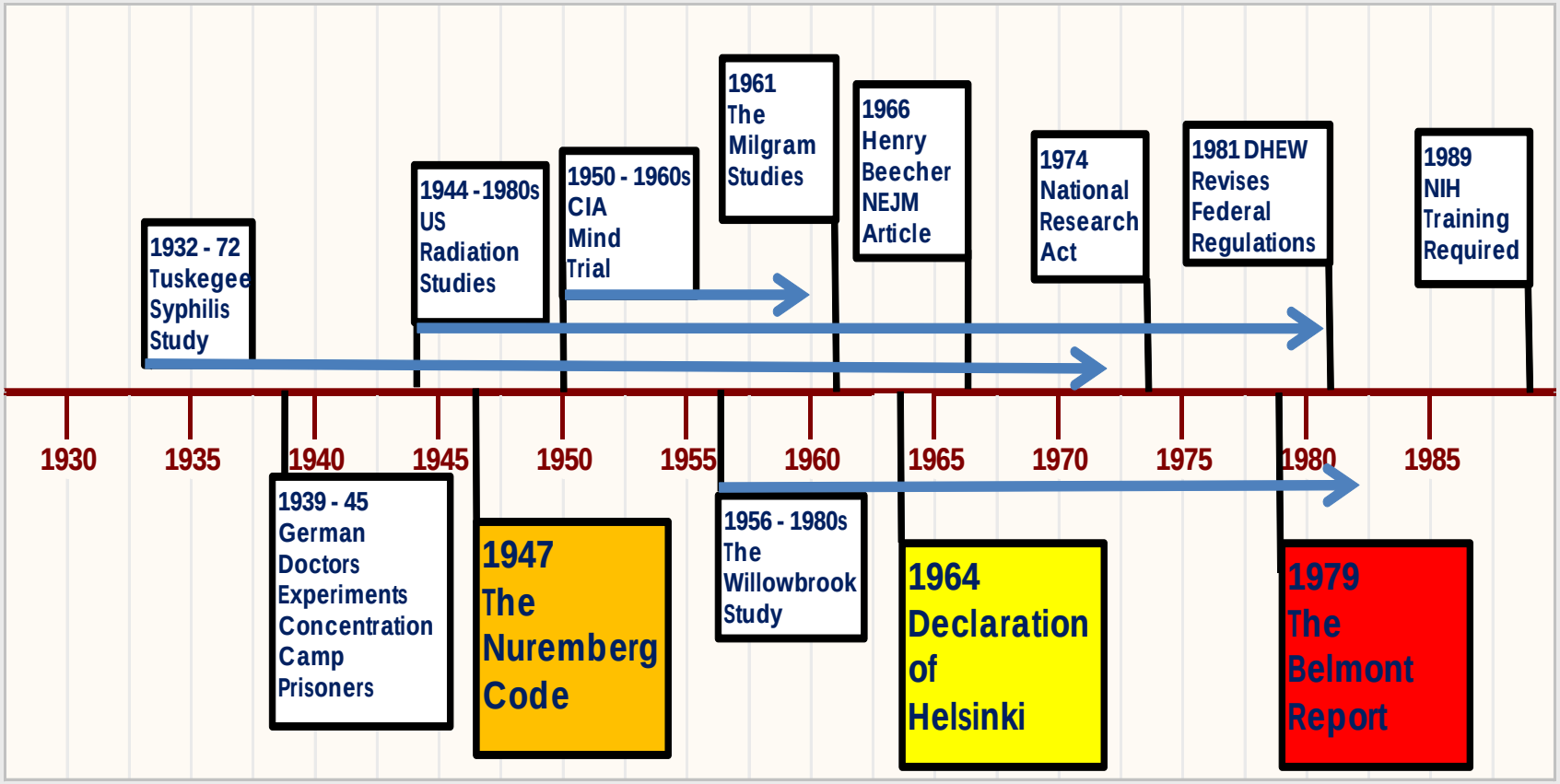
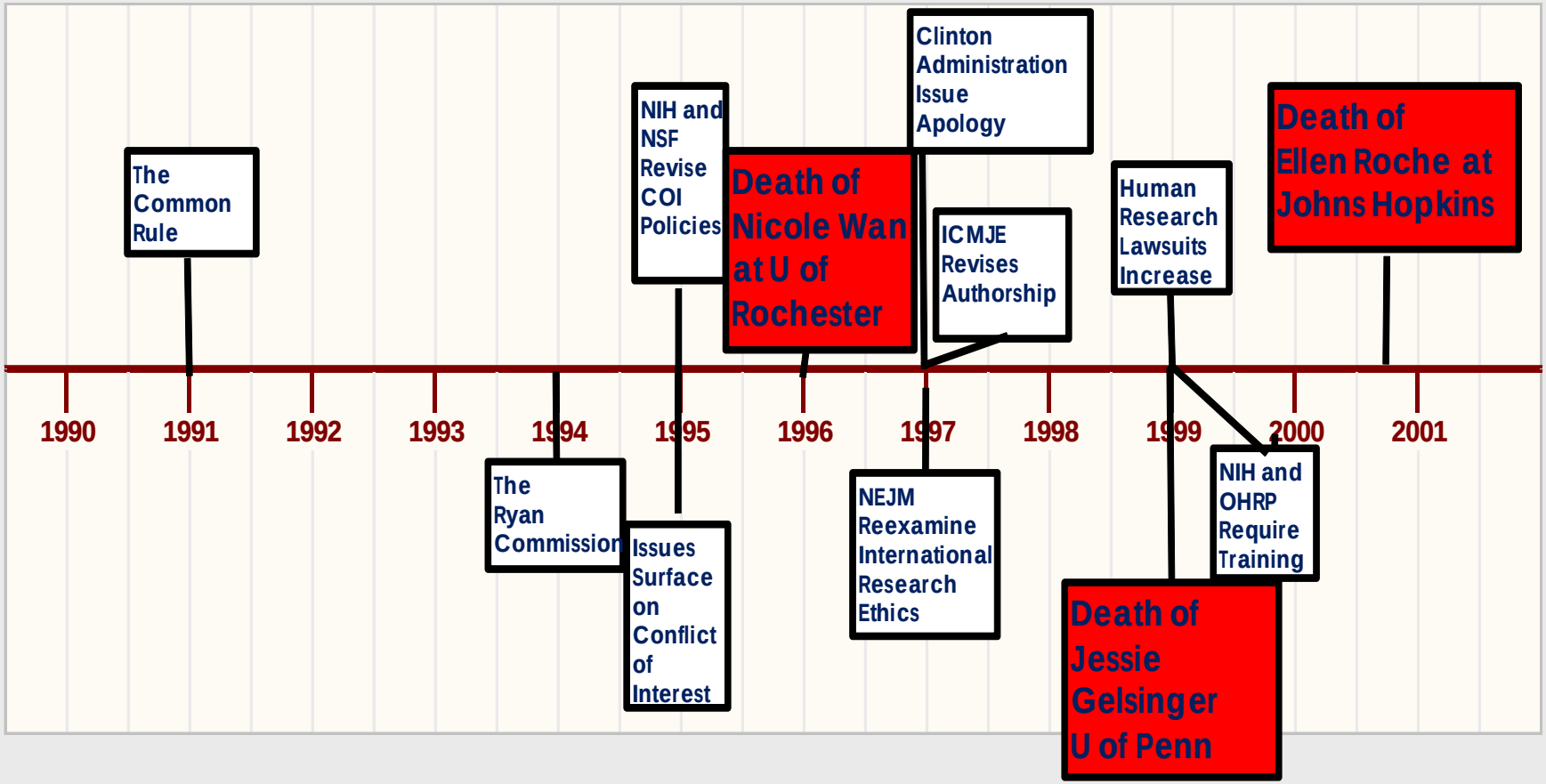
May 20, 2011

What is the history behind human subject protection?

Historical Events in Human Research



Historical Events in Clinical Research



Tuskegee Study of Untreated Syphilis

- In 1932, the Public Health Service, working with the Tuskegee Institute, began a study to record natural history of syphilis
- Involved 600 men – 399 infected with – 201 controls
- No Informed Consent
- Researchers told being treated for “bad blood”
- In exchange for participation:
  - Free medical exams
  - Free meals
  - Burial insurance
- Originally only to last 6 – 8 months – actually lasted 40 years

Tuskegee

- Subjects were not told of their disease
- Subjects were not offered treatment when available
- During the 40 years of this study, subjects and their families continued to be exploited

The Nuremberg Doctors

- At the beginning of WWII, Germany had the most scientifically and technologically advanced country

- Government supported midwifery, homeopathy, nutritional programs – first to ban smoking from public area and banned women from receiving tobacco ration during pregnancy

- BUT doctors exploited people's trust AND disguised discrimination and murder as public health and medical research

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Nuremberg Code

- August 1947 – verdict against 23 Nazi physicians
- Judgment included a set of standards
  - **The Nuremberg Code**
- The Nuremberg Code considered "*ethical yardstick*" that defendants were measured and their guilt determined

Nuremberg Code 1947

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

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 experiments 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.

Nuremberg Code 1947

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 a priori reason to believe that death or disabling injust will occur; except, perhaps, in those experiments where the experimental physician also serves as subjects.

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

Nuremberg Code 1947

7. Proper preparation 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.

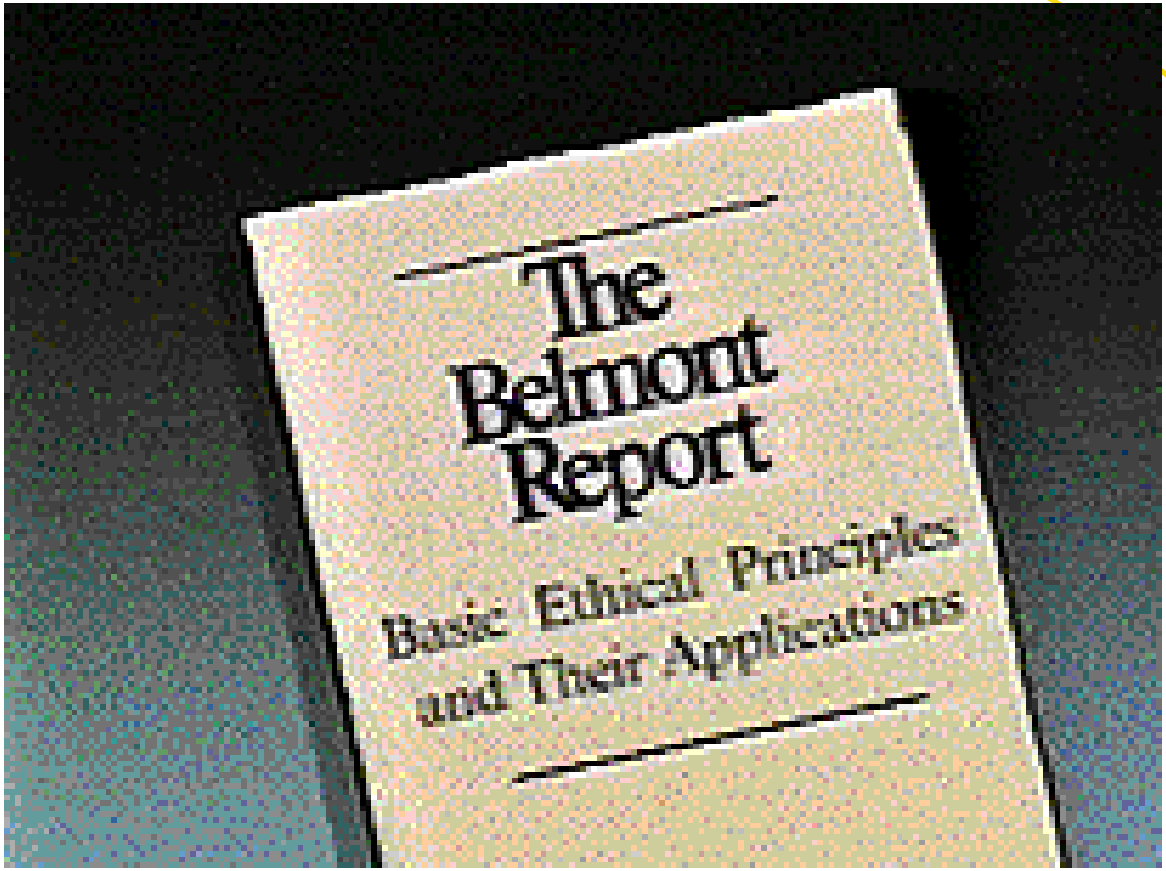
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

Nuremberg Code 1947

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

National Research Act 1974

- 1974 National Research Act – by Senator Kennedy and the 93rd Congress
  - Established the “National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research”
  - Required IRBs at institutions receiving federal support for human subjects research



Ethical Principles & Guidelines for Research Involving Human Subjects

National Commission for the Protection of Human Subjects
of Biomedical and Behavioral Research April 18,1979

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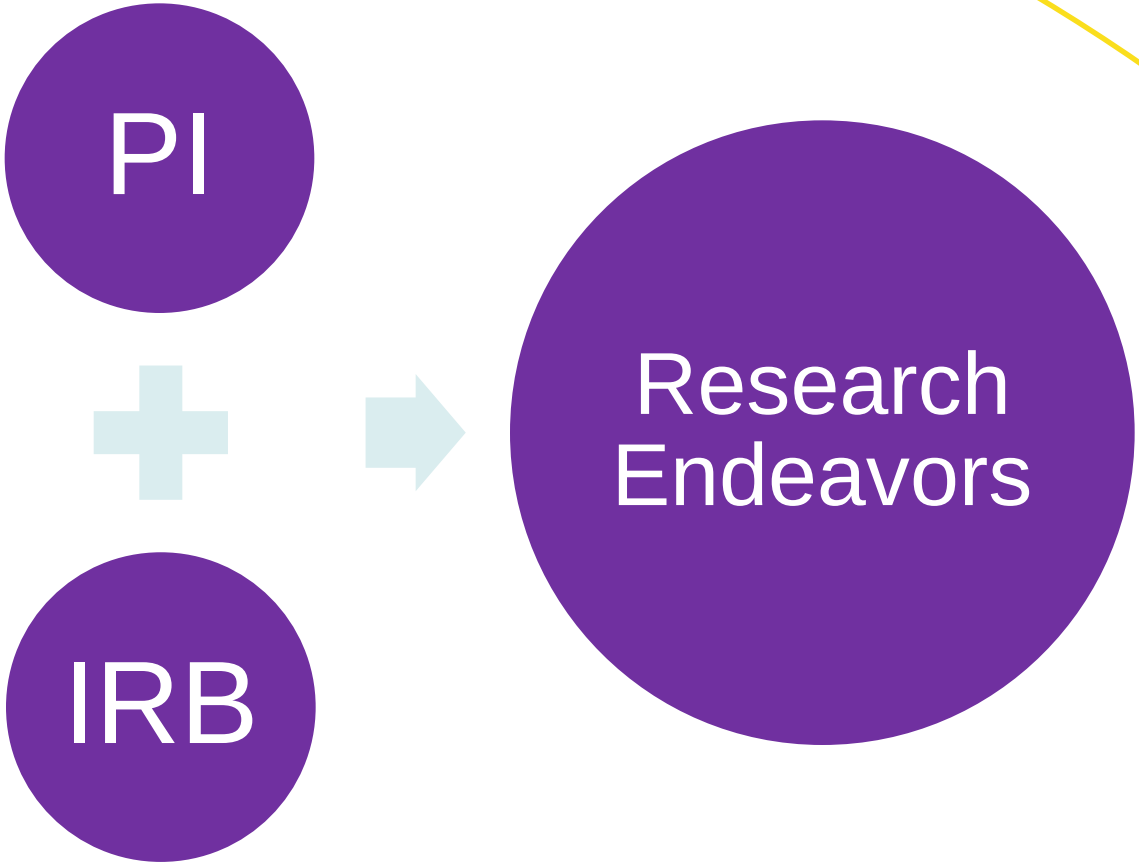
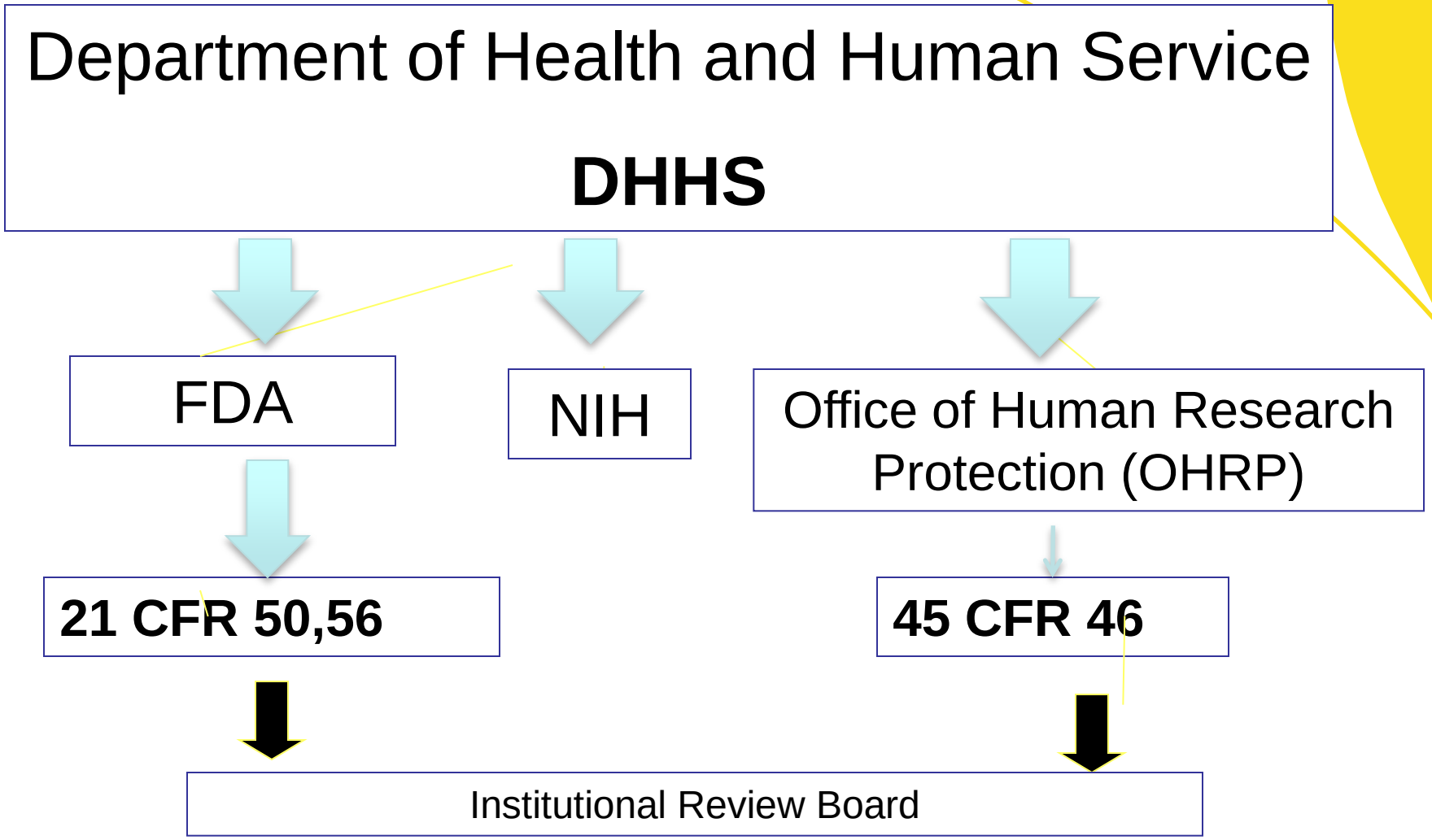
Basic Ethical Principles From The Belmont Report

- **Respect for Persons**
  - People treated as autonomy
- **Beneficence**
  - Risk/Benefit ratio is considered
- **Justice**
  - Burden of research does not fall on any one group of individuals



A Collaborative Relationship

The ability of the PI to work with IRB and for IRB to support the PI is critical for the safety of research subjects and for the successful completion of research.


Department of Health and Human Service
DHHS
FDA
NIH
Office of Human Research Protection (OHRP)
21 CFR 50,56
45 CFR 46
Institutional Review Board

Protecting human subjects

It’s not just the IRB’s responsibility anymore

Human Research Protections is a Shared Responsibility

Institutional Review Board

Office of Clinical Trials

Research Compliance

Sponsored Programs Administration

Institutional Official

Principal Investigator and Research Team

NYU Langone Medical Center

AAHRPP Reaccreditation

- Association for the Accreditation of Human Research Protection Programs
- First IRB in NYC to receive this initial accreditation in March 2003
- In April, we received reaccreditation for another 5 years

The Responsibilities of the IRB

Administrative and Oversight

The IRB Administrative Office

- Provides support to the IRB Boards
  - Three Boards – A, B, and C
  - Each has an Analyst, Manager, Coordinator and Assistant Coordinator
- Helps investigators in identifying and complying with all pertinent federal regulations and guidelines
- Education Office
  - Analyst for PI and research staff education
  - Coordinator for staff and IRB member education
- Quality Assurance and Quality Improvement
  - Manager for QI – performs audits when IRB requests
  - Continuous Quality Improvement Manager – new program to assist Principal Investigator Initiated Studies

IRB Oversight

- IRB is mandated to be autonomous in all aspects of decision-making

- IRB is a “franchise” of OHRP and FDA
  - NYU SoM had a Federalwide Assurance
  - Title 45 CFR Part 46 “Common Rule” that regulates IRB performance and decision-making for behavioral and biomedical research
  - Title 21 CFR Part 50 (FDA) regulates IRB performance and decision-making for drug and medical device research

Understanding the “spirit” of the federal regulations

Definitions and Review Methods

All definitions can be found in 45 CFR 46

What is *research*?

- Research is defined as:
  - A ***systemic investigation***, including research development, testing and evaluation, designed to develop or contribute to ***generalizable*** knowledge.

- ***Systematic Investigation***
  - Activity conducted according to plan – the protocol
  - Intent or purpose to draw logical conclusion
- ***Generalizable***
  - Extrapolate from specific cases to more general cases beyond immediate protocol
  - Contribute to knowledge base of a research area

Does the research involve *human subjects?*

- A living individual about whom an investigator (whether professional or student) conducting research obtains
  - Data through interventions or interactions with individual

- A living individual about whom an investigator conducting research obtains
  - Identifiable private information

What is an IRB?

- ***IRB*** – means an institutional review board established in accord with and for the purposes expressed in this policy

- ***IRB Approval*** – the research has been reviewed and has been approved and will be conducted within the constraints set forth by the IRB, the institution and the federal regulations

IRB

- At least 5 members
- Varying backgrounds
- Sufficient experience
- Diversity within the membership
- A community member
- Members who have a conflict of interest with project being reviewed will excuse themselves
- All votes are confidential – the decision regarding the specific project are made as a “Board” – not individually

What is the *risk* to the subject?

- Minimal risk
  - The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physician or psychological examinations or tests.
  - Risk is NOT assessed based on disease condition

Review Methods

Risk:	Less Than	Minimal	Greater Than
Review:	***Exempt***	***Expedited***	***Full Board***
Regs:	6 Review Categories	7 Review Categories	

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Exempt Categories

1. Educational practices

2. Educational tests, surveys, questionnaires, interviews, observational **not for studies for minors*

3. Surveys, questionnaires, interviews, observational studies of public officials

4. Existing data, documents, recordings, pathological or diagnostic specimens

5. Demonstration Projects under HHS

6. Taste and food quality evaluation and consumer acceptance studies

Determination of Exemption

- Needs to be made by a trained professional
  - Instructions found on our web site
- PI can use the regulations to determine research falls under exemption category
- BUT needs to be verified by IRB.
  - IRB Web site provided guidance and direction

Expedited Review

Research activities that present *no more than minimal risk* to human subjects and fall within the expedited review categories, found 45 CRF 46.110

Expedited Categories

1. Clinical studies of drugs and medical devices only when conditions are met

2. Collection of blood samples by finger stick, heel stick, ear stick or venipuncture with restrictions

3. Prospective collection of biological specimens for research purposes by noninvasive means

4. Collection of data through noninvasive procedures routinely employed in clinical practice

5. Research involving materials (data, documents, records or specimens) that have already been collected, or will be collected solely for nonresearch purposes

6. Collection of data from voice, video, digital or image recordings made for research purposes

Expedited Category 7 – most applicable for SBR/CBR

7. Research on individual or group characteristics or behavior including, but not limited to:
   - research on perception
   - cognition
   - motivation
   - identity
   - language
   - communication
   - cultural practices
   - and social behavior

- or research employing
  - survey
  - interview
  - oral history
  - focus group,
  - program evaluations,
  - human factors evaluations,
  - or quality assurance methods

Expedited Review

- Meets federal criteria for *minimal risk*
- Meets 45CFR46.111 findings

Full Board Review

- MORE THAN minimal Risk

- Examples:
  - Experimental Drug Studies
  - New Combination of Approved Drugs
  - Experimental Device Studies
  - Projects that do not fit into the Expedited categories

Obtaining IRB Approval “The 111 Findings”

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefit
- Selection of subjects is equitable
- Informed consent will be obtained
- Informed consent will be documented
- Adequate monitoring to ensure safety
- Privacy is protected
- Vulnerable populations have been additionally safeguarded

Submission to the IRB

There are tools available for you to follow and a phone number for you to call if you have questions.

☺

The Protocol

- Characteristics of the Research Population
- Methods and Procedures
- Risk/Benefit Assessment
- Investigator's Qualifications and Experience
- Subject Identification, Recruitment and Consent/Assent

Informed Consent

- A **description of any reasonably foreseeable risks** or discomforts to the subject.
- **Participation is voluntary** without negative consequences if you don’t participate.
- It is a PROCESS, not the signing of a form
- Follow the NYU IRB Template
- Write in nonscientific language your community members will understand.

The Application

- Exempt
- Expedited
- Full Board

- Complete the entire application

- Attach any items for subjects as appendix – IRB needs to approve ***all*** items that go to the subject
  - Surveys, questionnaires
  - Does the data need to be monitored?

When research goes wrong

The story of Jessie Gelsinger and the U of Penn

Jessie Gelsinger

- In 1999, a young man, who had just turned 18 decided to participate in a clinical trial
- He had a mild form of a genetic metabolic disease – OTC – where his body could not metabolize ammonium.
- Jessie spoke with his dad about this and they decided to do this – he wanted to help

Jessie Gelsinger

- **1981**
  June 18: Jesse Gelsinger is born
- 1983
  Jesse is diagnosed with the non-fatal form of OTC deficiency.
- **1992**
  James M. Wilson founds a for-profit, private firm named Genovo, Inc., which will, by 1999, provide $4.7 Million annually (of a $22 million budget) to the Institute for Human Gene Therapy at the University of Pennsylvania, which Wilson also directs. Dr. Wilson is a major shareholder of Genovo.
- **1993**
  April: Mark Batshaw and Wilson begin experiments on OTC deficient mice. Eventually they demonstrate the efficacy of the adenovirus as a vector for the OTC gene, but the results of safety studies on mice, rhesus monkeys, and baboons give mixed results. Three monkeys die from an early, stronger version of the vector, then others suffer severe hepatitis from the same one Jesse would receive.

Jessie Gelsinger

- **1994**
  Batshaw and Wilson seek advice from the University's resident bioethics expert, Arthur Caplan, about how to select human subjects for the next phase of the adenovirus research. Caplan advises against using babies dying from OTC deficiency, in favor of asymptomatic, adult patients like Jesse. The researchers begin scouting for possible volunteers for the clinical trial.
- **1995**
  Mid-year: The Recombinant DNA Advisory Committee of the National Institutes of Health approves the Batshaw-Wilson protocol, with two dissenting experts stating that it is too risky for asymptomatic volunteers (such as Jesse).
- **1998**
  December: Jesse suffers a severe bout with the disorder because he has strayed from his regimen of medications. He is hospitalized and becomes comatose, but then recovers.

Jessie Gelsinger

- **1999**
  June 18: The Gelsinger family flies to Philadelphia for Jesse's screening at the Hospital of the University of Pennsylvania. They take in the tourist sites. It is Jesse's 18th birthday.
  June 22: Jesse qualifies for the Batshaw-Wilson study, with a blood-ammonia reading of 47 micromoles per liter, which is below the maximum of 75 specified by the protocol. Normal ammonia is 35. Jesse is thrilled, and he returns home to Arizona.
  September 12: Jesse reports for duty at the University. His blood-ammonia reading is 91 micromoles. Although this reading far exceeds the limit set by the protocol, the experiment proceeds.
- *September 13, 10:30 a.m.*: Jesse's hepatic artery is injected with 30 milliliters of the genetically altered adenovirus and he is given medications that reduce the ammonia level in his blood. After 2 hours, the ammonia reading drops to 60. The surgeon who performs all this work is Steven E. Raper.
- *September 14*: After the 20th hour of the experiment, Jesse develops jaundice (turns yellow) because of a certain clotting disorder that was already observed in the dead rhesus monkeys earlier in this research. He sinks into a coma, then into "multiple organ system failure," and is placed on life-support.

Jessie Gelsinger

- *September 17*: Jesse is found to be brain-dead, removed from life support, and pronounced dead. At least nine family members are present.

- *September 28*: The University of Pennsylvania announces that Jesse died as the result of a gene-therapy experiment, and the story is reported world-wide.

- *October 11*: The US Food Drug Administration forbids any new subjects from entering all other there were two ongoing trials that are similar to the Batshaw-Wilson study, but those already under treatment are allowed to continue.

- *November 3*: The Washington Post reports that researchers and drug manufacturers have failed to inform the National Institutes of Health of 6 deaths that have occurred in gene-therapy experiments since April 1998.

Jessie Gelsinger

- *November 9-10*: Public hearings are held at the NIH's headquarters in Bethesda, MD on Jesse's case. Batshaw, Wilson, and Raper begin to admit to discrepancies between the research protocol and their performance, but still defend their conduct. Government officials from the Recombinant DNA Advisory Committee cite the researchers for:

  - Removing language from the consent forms that described animal deaths and sickness earlier in the research;
  - Failing to promptly report that two volunteers in the study suffered severe reactions at dosages lower than the one Jesse received (they reported this 2 months later, and proceeded with higher dosages without consulting FDA);
  - Changing the order of the patients without asking permission (Jesse was second in his set of three, but as the male subject he was supposed to be third).
  - Proceeding with the experiment when Jesse's ammonia reading exceeded the maximum allowed by the protocol.
  - Paul Gelsinger speaks at the hearing, urging all parties to draw positive results from his son's death. Through this point in the ordeal, he has stated that he does not hold the researchers responsible for the tragedy. **2000**

Jessie Gelsinger – Ethical Considerations

- COI – Was Dr. Wilson able to be objective with a major financial stake in the company who makes the vector? Also, U Penn had a stake in the company, too – could that have clouded their oversight?

- Could an 18-year old truly give informed consent for a clinical trial with so much risk and so little benefit?

- In Letters of Determination from OHRP, it found that the protocol was not followed AND the fellow/residents took it upon themselves to review adverse event data and make decisions – where were the PI's during this time?

Credits

- * Wolf, Leslie E. (2010). The Research Ethics Committee Is Not the Enemy: Oversight of Community-Based Participatory Research. *Journal of Empirical Research on Human Research Ethics: An International Journal*, Vol. 5(4), pp. 77 - 84

Reference

- http://www.hhs.gov/ohrp/ - Office of Human Research Protection
- http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html - 45CFR46
- http://www.nmmu.ac.za/documents/rcd/The%20Belmont%20Report.pdf
- http://www.hhs.gov/ohrp/policy/exprev.html - Expedited Categories
- http://irb.med.nyu.edu/ - NYU SoM IRB
- http://irb.med.nyu.edu/forms-guidance/guidance-submission - IRB Forms
- http://irb.med.nyu.edu/for-researchers-0 - Information for Researchers

Questions???

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To add additional section divider slides, go to Insert → Duplicate Slide