North Shore-LIJ Health System

PREP COURSE #1

What Needs IRB Review?

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Course Director, Kevin Tracey, has disclosed a commercial interest in Setpoint, Inc. as a board member, for stock, and consulting support. He has resolved his conflicts by identifying a faculty member to conduct content review of this program who has no conflicts.

Hallie Kassan has nothing to disclose
Marilyn Dienstag has nothing to disclose
Human Research Protection Program

Office of Research Compliance (ORC)  Office of the Institutional Review Board (OIRB)

The ORC and OIRB work together to protect the rights, welfare and privacy of research participants
Human Research Protection Program

Office of Research Compliance (ORC)

• Education and training
• On-going audits for Good Clinical Practice (GCP)
• Respond to allegations or audit findings of improper/illegal activities and enforcement of disciplinary action for violations
• Regulatory support for investigator-initiated studies
Human Research Protection Program

**Office of the Institutional Review Board (OIRB)**

- Administration of the NS-LIJ Institutional Review Boards responsible for the oversight of human subjects research
- Guidance and support to investigators who plan to conduct clinical research projects
- Development of policies and procedures to assure compliance with institutional and governmental regulations
- Review and approve all human subjects research
Learning Objectives

• Identify the ethical cases which have led to the Human Subject Protection Program
• Identify federal and state regulations applicable to human subjects research
• Differentiate between activities considered research with human subjects and those not
Where Did the Research Regulations Come From?

(From Dunn and Chadwick, 1999)

Research Ethics Milestones

- National Bioethics Advisory Commission 1995
- Common Rule 1991
- CIOMS Guidelines 1982
- Consolidated HHS/FDA Regulations 1981
- Belmont Report 1979
- Declaration of Helsinki 1964
- Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act 1962
- Milgram Study 1966
- The Syphilis Study (Exposé) 1966
- The Beecher Article (NEJM) 1966
- The Thalidomide Tragedy 1961
- Human Radiation Experiments
- The Nazi Experiments
- The Syphilis Study (Begins)

Trigger Events

- Nuremberg Code 1947
Nazi Atrocities

- Human Experimentation in Concentration Camps
  - Freezing Experiments
  - Typhus Infections
  - Twin Experiments
Nuremberg Trial

- In 1946-47, the Nuremberg Military Tribunal uncovered the atrocities of Nazi human research.
- Nazis who conducted these experiments on prisoners in Concentration Camps, were tried for War Crimes and Crimes Against Humanity.
Nuremberg Code

- Voluntary Consent
- Sound Study rationale – sound scientific basis, and for good of society
- Risk/Benefit – avoid suffering
- Protect Human Subjects
Nuremberg Code

• Generally held as the first international ethical code for the protection of human research subjects.
• Not widely distributed or followed throughout the world.
• *The Nuremberg Code* was believed to apply to the Nazi doctors, not to other researchers.
• Abuses of human subjects continued to occur in the 1940’s-1960’s.
Drug Amendments of 1962

• Proof of efficacy

• Inform subjects of drug’s experimental status

• Obtain written consent

• Adverse drug reactions required to be reported to FDA
Stanley Milgram Experiment

• Occurred between 1961-1963
• Claimed to study memory, but actually evaluated obedience to authority
• Subjects were assigned the role of “teachers” and told to quiz other research subjects (“learners" whom they could not see)
• The teachers were instructed to deliver increasingly powerful electric shocks for every wrong answer
Milgram Study

The experimenter (E) persuades the “teacher” (S) to give shocks to the “learner” (A) in response to incorrect answers.
**Milgram Study**

- 60% of the “teachers” were persuaded to give shocks up to the highest level, even after the “learner” (actor) appeared to lose consciousness.

- At the study debriefing, many of the “teachers” justified their actions by saying they were only following instructions.
Milgram Study

• “I observed a mature and initially poised businessman enter the laboratory smiling and confident. Within twenty minutes he was reduced to a twitching, stuttering wreck, who was rapidly approaching a point of nervous collapse.”

Stanley Milgram - Obedience to Authority
Milgram Study

- Criticism focused on:
  - Extreme psychological stress
  - No informed consent
- Impact on federal regulations:
  - Deception allowed but only in limited conditions and only with IRB approval
  - In addition to physical harms, investigators and IRBs must consider other harms including psychological, social, legal and economic
U.S. Public Health Service Study of Untreated Syphilis at Tuskegee 1932-1972

- Subjects were 600 Black men
- Promised free transportation to and from hospitals, free hot lunches, free medical care for diseases other than syphilis, and free burial after autopsies were performed.
- Never informed that they were research subjects, or that treatment for their syphilis could have been provided.
- Told they had “bad blood”, and required periodic medical examinations, including spinal taps.
Tuskegee Syphilis Experiment

- Subjects were not offered information regarding the available treatment, and were actively prevented from seeking it elsewhere.
- Some subjects died of the disease, passed it on to wives, or passed congenital syphilis to children.
U.S. Public Health Service Study of Untreated Syphilis at Tuskegee 1932-1972

‘NOW can we give him penicillin?’
Study of Untreated Syphilis in Negro Males

- Resulted in passage of the National Research Act (1974)

- Established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

- Belmont Report (ethical principles)

- DHHS & FDA Regulations
National Research Act of 1974
National Research Act of 1974

- On July 12, 1974, the National Research Act was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The NRA also mandated the creation of Institutional Review Boards (IRB’s) for all research that receives direct or indirect funding from the Department of Health and Human Services.
Belmont Report

• Differences between Research and Clinical Practice

• Identified basic ethical principles which underlie the ethical conduct of research involving human subjects
  • Respect for persons.
  • Beneficence.
  • Justice.
Boundaries Between Research & Practice

- **Practice**: interventions that are designed solely to enhance the well-being of a client and have a reasonable expectation of success.
- **Research**: Activity designed to test a hypothesis, permit conclusions to be drawn, contribute to generalizable knowledge.
- Research and Practice can be done together, but there is a Potential Conflict:
  - When a subject’s participation may place him/her at risk of harm.
Respect for Persons = Informed Consent

1. Informed Choice

• Acknowledges the freedom and dignity of every person.
• People should be able to choose what shall and shall not happen to them.
• Requires obtaining informed consent from all potential research subjects.
Respect for Persons

2. Persons with diminished ability to consent are entitled to protection.
   • The extent of protection required depends on the risk of harm and the likelihood of benefit.
   • Even these persons should be informed about the study, and *assent* to the extent possible.

3. That true informed consent has been obtained is the responsibility of the investigator.
Beneficence = Risks and Benefits

1. Do no harm
   • One should not injure a person despite possible benefits to others (society).
   • Risks to subjects should be minimized.

2. Maximize Benefits/Minimize Harms
   • Beneficence recognizes the long-term benefits that arise from improving knowledge and medical care.
Justice = Enrollment

- Justice requires equitable selection, recruitment, and fair treatment of research subjects.
  - Subjects should not be selected because of easy availability or vulnerability.
  - Research should not provide benefits only to those who can afford them.
  - Research should not unduly involve subjects from groups unlikely to benefit from such research.
  - Groups of subjects should only be included or excluded from research for scientific reasons.
How did the Tuskegee Study violate these principles?

• Respect for Persons
  No informed consent process.
  Deception – participants were told that non-therapeutic spinal taps were “treatment” for “bad blood”.

• Beneficence
  Withholding effective treatment.
  Lack of meaningful and effective continuing review.

• Justice
  Vulnerable population was used.
Today’s Research Climate
Jesse Gelsinger

In September 1999, 18 year old Jesse Gelsinger died after participating in a gene therapy trial at the University of Pennsylvania.
FDA Findings

• Unreported adverse events
  • Four prior volunteers had experienced liver damage

• Inadequate informed consent
  • Risks were not fully explained

• Eligibility violation
  • Jesse’s ammonia levels were too high

• Conflict of interest
  • Penn and Dr. Wilson (PI) had financial interest in the vector that was used
Outcome

• One teenager dies
• The U Penn gene research facility is closed
• DHHS/NIH take a hard look at conflict of interest policies
A healthy volunteer died recently after inhaling a drug in a federally financed asthma study conducted by Johns Hopkins University, officials said yesterday. The volunteer’s hospitalization after inhaling the drug led the the institution to suspend the research.
May 4  Ellen Roche inhales hexamethonium
May 5  Develops cough, shortness of breath, aches
May 7  Lungs functioning at two-thirds capacity
May 9  Hospitalized for observation
May 12  CAT scan reveals severe lung damage
June 2  Death from ARDS
Principal Investigator

- Failed to obtain published literature about the known association between hexamethonium and lung toxicity.
- Use of hexamethonium is not currently approved by the FDA for use in humans, and has never been approved by the FDA for administration via inhalation.
- Implemented changes to the protocol without notifying the IRB
Informed Consent Document

- Failed to adequately describe research procedures
- No mention that hexamethonium was experimental
PI: Failed to report AE

April 23  First subject inhales hexamethonium. Develops cough that lasts from April 25 to May 3

May 5  Ellen Roche inhales hexamethonium -

May 7  Develops cough, shortness of breath,

May 9  Hospitalized

June 2  Death from ARDS
Johns Hopkins IRB

- Failed to adequately assess risks
- No required discussion by the whole IRB of each proposal
- Concerns reviewed separately by subcommittee
OHRP Conclusions

• An adequate evidence base did not exist for the IRB to be confident that inhaled hexamethonium was safe for use in research subjects

• The consent form for the research should not have been approved by the IRB
Johns Hopkins
Research on Hospital Infections
Johns Hopkins Checklist Project

• The program involved a simple, five-step checklist to remind physicians of things to do before implementing certain procedures.

• Physicians should carry out routine precautions, for example washing their hands and wearing a sterile gown and gloves.
Johns Hopkins Checklist Project

• After three months of using the checklist, the rate of bloodstream infections from the central lines was decreased by two thirds

• Researchers estimated that in the 18-month period following implementation of the checklist, the program saved more than 1,500 lives and nearly $200,000,000
Johns Hopkins Checklist Project

• The Office for Human Research Protections (OHRP) halted the program.

• Johns Hopkins was required to discontinue its plans to extend the program to hospitals in New Jersey and Rhode Island.
1. "...human subjects research was to be carried out at the Michigan hospitals and that care would be changed as a direct result of the research."

2. "...the JHU IRB approved the project as exempt under exemption 4 (HHS regulations at 45 CFR 46.101(b)(4))....OHRP notes that the research proposed in the application to the JHU IRB and described in the above-referenced publication involved testing an intervention in the ICU setting and not just the collection or study of data, documents, or records, and the data, documents, and records that were collected and studied did not exist until after the research was proposed to the IRB."

3. "...Although JHU asserts that the interventions carried out by the Michigan hospitals were not human subjects research, but quality improvement activities, OHRP notes that quality improvement activities can also be research activities."
Why do we do what we do?

“There is much to be gained from research, but even great benefits cannot come at the cost of adequate respect for individuals. Real people, with real lives, make research possible. They deserve real protection.”

Jeffrey P. Kahn, PhD., MPH
Director, Center for Bioethics
University of Minnesota
Regulations
Federalwide Assurance (FWA)

• Formal agreement between NS-LIJ and the DHHS OHRP
  – Documentation of commitment to operate in compliance with the federal regulations governing research with human subjects
  – Statement of commitment to conduct research within the ethical standards outlined in the *Belmont Report*
  – Applies to all research involving human subjects regardless of source of funding or support conducted at NS-LIJ, as well as to research conducted elsewhere by physicians, students, staff, or other representatives of the NS-LIJ in connection with their institutional responsibilities
45 CFR 46 – The Common Rule
Protection of Human Subjects

• Outlines criteria for approval of research and requirements for the informed consent process
• Defines special requirements for vulnerable populations
• Defines composition of IRB Committee

• [http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm)
FDA regulations

- 21 CFR 50 - Protection of Human Subjects
- 21 CFR 56 - Institutional Review Boards
- 21 CFR 312 – Investigational New Drug Application
- 21 CFR 812 – Investigational Device Exemptions

- [www.fda.gov](http://www.fda.gov)
HIPAA

- 45 CFR 164
- IRB serves as the privacy board to assure research studies are in compliance with HIPAA regulations
  - [http://www.access.gpo.gov/nara/cfr/waisidx_07/45cfr164_07.html](http://www.access.gpo.gov/nara/cfr/waisidx_07/45cfr164_07.html)
NY State Law

• Public Health Law Article 24A
• Protection of Human Subjects
What Type of Activity Needs to Be Submitted to the IRB?
Definitions
What Is Research?

“A systematic investigation designed to develop or contribute to generalizable knowledge.”

-- 45 CFR 46.102(d)

“[…]the term ‘research’ designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge...Research is usually described in a formal protocol that sets forth an objective and a set of procedures to reach that objective.”

-- Belmont Report
What Is a Human Subject?

• “A living individual about whom an investigator...conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.”
  -- 45CFR46.102

• “An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.” -- 21CFR50.3

*Note: New York State law does not distinguish between living and deceased individuals in its definition of human subject.
IRB review and approval is required PRIOR to initiation of all research involving human subjects.
Is It Research?

- Quality Assurance or Quality Improvement projects.
- Chart reviews.
- Use of discard specimens.

Even though patient care is not altered, it may still be research!
Research vs. Standard Care

“The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy or procedure)[...]”
Quality Management/Quality Improvement (QM/QI) Activities vs. Research Activities Subject to IRB Review

• The intent of quality initiatives is to improve processes of care and patient outcomes by establishing evidence-based standards of care and continuously measuring performance compared to established benchmarks and goals

• Guidance available at www.nslij.com/irb
QM/QI Initiatives

Examples of Activities not considered research at NSLIJ:

- Any hospital QI initiatives, and presentation/publication of results, that are conducted within NSLIJ only, and that serve to develop a standard of care or benchmark for applicability within NSLIJ

- Submission of data to a national or state registry/database that is mandated at the state or federal level

- Hospital QI use of data from a registry/database, meeting any of the criteria above, for the purpose of improving NSLIJ’s ability to meet or exceed an existing national standard of care or benchmark.
QM/QI Initiatives

Any QI/QM projects that are **NOT** considered research, have to be vetted through, and endorsed by, Health System’s Quality Management program and/or a hospital quality management department.
Research Activities

The following activities are considered research activities.

• Any hospital QI initiative, conducted within NSLIJ, designed to develop a standard of care for general applicability (i.e., not only for operations within NSLIJ, but to outside entities as well).

• Any QM or QI initiatives (including those proposing to develop an operational standard of care of benchmark) that are “investigator-initiated”, i.e., that have not been vetted through, and endorsed by, Health System’s Quality Management program and/or a hospital quality management department.

• Any activity that proposes comparisons of one or more prospective interventions that are deliberately administered (through a randomization or other process) to some patients (if within NSLIJ) and not to others.
If It’s Human Subjects Research, What Do You Do?

Determine what category your research falls into.

– Exempt.
– Expedited.
– Full board review.
Categories of Review

- Exempt
- Expedited
- Full

Risk Levels:
- Minimal risk
- Higher risk
Categories of Research Review

• Full Board – Studies that are greater than minimal risk
  – Investigational drug studies, Investigational device studies, randomized drug trials

• Expedite – Minimal risk studies – Do not get reviewed by the full IRB Committee
  – Retrospective chart reviews, blood draws, ultrasound studies, buccal samples

• Exempt - Minimal risk studies - Do not get reviewed by the full IRB Committee
  – Types of surveys, retrospective chart reviews without identifier collection
IRB Responsibilities

• Determine whether proposed research exposes subjects to unreasonable or unnecessary risk.
• Review informed consent process and forms.
• Monitor progress of research.
What Governs the IRB’s Decision-making?

- Federal regulations
- State regulations
- Institutional policy
- The Belmont Report
- Terms of our Federalwide Assurance (FWA)
- Other mandates (HIPAA, NIH, etc.)
What Criteria Does the IRB Use to Review a Research Study?

Federal regulations mandate that the IRB ensures that:

- Risks to subjects are minimized.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
What Criteria Does the IRB Use to Review a Research Study?

- Is subject selection equitable?
- Will informed consent be sought?
- How will informed consent be documented?
- Are there provisions to protect the privacy of subjects?
- Are there additional safeguards for vulnerable populations?
“The key lies in having everyone at the institution embrace the idea that federal regulations are in place for good reason – patient safety.

We have to have a culture in which everybody is trying to do the right thing, the right thing all the time.”

Edward Miller
Dean and Chief Executive Officer
Johns Hopkins Medicine
Is this human subjects research?

An adult with ADHD presents to their physician. To date, no behavioral or drug intervention has proved useful. The physician has read several reports about a drug that is approved and labeled for another indication but has shown some benefit for ADHD. The physician wants to prescribe this drug for this patient.
Is this human subjects research?

A drug is approved and sold in a solid tablet to treat adults (18 and older) for diabetes. A physician would like to study the effect of this same drug in a liquid formulation in children 10-17, with diabetes.
Is this human subjects research?

• An investigator will purchase a commercially available cell line to study the effects of a drug on heart cells.
Is this human subjects research?

• To study the course of disease, an investigator will collect identifiable biopsy samples from pathology and match the samples up with data in the patient’s medical record.
Is this human subjects research?

• A new nursing training program has been implemented in the Cardiology Unit. The nurse manager will perform evaluations to determine the impact of the training program on work performance at NS-LIJ.
Is this human subjects research?

• Blood will be drawn from employees of the Health System, to compare the blood of healthy people to that of patients with Parkinson’s disease
Is this human subjects research?

• A physician will send a survey to all surgeons at NS-LIJ to elicit their experience with fires occurring in the operating room. No information about the surgeon will be obtained in the survey.
Is this human subjects research?

• A physician would like to collect data from patients’ medical records and submit it to the manufacturer of the drug that the patients are taking, on an on-going basis. The data will be used to determine long term effects of the drug.
Is this human subjects research?

- A physician would like to collect medical record data from all patients in a database. In the future, data from this database will be used for research studies. However, those studies have not yet been designed.
Is this human subjects research?

• A physician would like to review the records of two patients with a rare disease and publish a paper on the course of the disease.
Questions??
Contact the IRB

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