Welcome to our September METS

• Please make sure your microphones are muted
• There will be a Q&A session after this presentation
  ○ Please reserve your questions until then
  OR
  ○ Put any/all questions in the chat and we will address them after the presentation
• This session may be recorded
IRB 101: Regulating Research

Research Ethics and the Responsible Conduct of Research
Human Subjects Research Ethics

Researcher responsibility to be honest and respectful to all individuals who are affected by their research studies or their reports of the studies’ results

At every step of the process:
- Responsibility to ensure the welfare and dignity of human and non-human participants/subjects in the study
- Responsibility to the discipline of science to be accurate and honest in public reports
Why Ethics?
The Nuremberg Trials (1946-47)

- The Doctors’ Trial exposed Nazi experimentation on human subjects
  - Infection of soft tissues
  - Freezing/hypothermia studies
- Laid the groundwork for today’s psychological and medical ethical standards
1. Voluntary consent of human subject is essential
2. The experiment must be necessary and yield fruitful results for the good of society
3. The experiment must be designed and founded on prior knowledge so that the anticipated results will justify the performance of the experiment
4. Avoid all unnecessary physical and mental suffering/injury
5. No experiment should be conducted when you know death or a disabling injury will occur (unless the experimenters also participate!)
6. The risk should never outweigh the benefit
7. Protect the participants from even remote possibilities of injury, disability, or death
8. The experimenter must be qualified to conduct the experiment
9. The subject has the right to terminate his/her involvement at any point during the experiment
10. The experimenter must be willing to terminate the experiment when/if he suspects injury, disability, or death might occur
No more unethical studies, right?

Wrong.
A Brief History of Human Subjects Violations

1932-1972
Tuskegee Syphilis Study
"Public health study" conducted in Alabama between 1932-1972 on poor, rural African-American men

1951
HeLa Cells
Young Black woman treated for cervical cancer by a doctor at Johns Hopkin who cultured them without her consent

1946-1948
STD Inoculation Study
"Public health study" in Guatemala to study penicillin efficacy
Gonorrhea and syphilis injected into 696 subjects: Prisoners, mental patients, orphans

1953-1973
Project MK Ultra
Government-sanctioned human experimentation program conducted under the guise of national security

1961-1963
"Obedience" Experiments
Exploration of how Nazi soldiers were able to commit atrocities because they were "listening to orders"

1971
The Stanford Prison Experiment
How does playing a role change one's behaviors?
A Brief History of Human Subjects Protection

- 1966: Ethics and clinical research by Henry Beecher
- 1972
- 1974
- 1979
- 1981
- 1991
A Brief History of Human Subjects Protection

1966: Ethics and clinical research by Henry Beecher

1972: AP reporter Jean Heller breaks Tuskegee Syphilis Study story

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- **1966**: Ethics and clinical research by Henry Beecher
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  - Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- **1979**:
- **1981**:
- **1991**:

Weill Cornell Medicine
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- **1979**: Belmont Report
- **1981**:
Advisory Panel
Convened in 1972
The Belmont Report
Basic Ethical Principles

- Respect for Persons
- Beneficence
- Justice
Respect for Persons

- Individuals should be treated as autonomous agents
- Persons with diminished autonomy are entitled to special protection
- Application:
  - Requirements of voluntary, informed consent
  - Maintain confidentiality and privacy
  - Extra protections for vulnerable populations

§46.111 Criteria for IRB approval of research.

(4) Informed consent will be sought from each prospective subject or the subject’s legally authorized representative, in accordance with, and to the extent required by, §46.116.

(5) Informed consent will be appropriately documented or appropriately waived in accordance with §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.
Beneficence

- Two general complementary rules:
  - Do no harm
    - All research has the prospect of harm, even if minimal
  - Maximize possible benefits and minimize possible harms

§45.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

1. Risks to subjects are minimized:

   (i) By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and
   (ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

2. 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. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
Justice

• Fairness in the distribution of the benefits and burdens of research
  o Seeks to guard against the unfair selection of research subjects because of their availability, compromised position, or manipulability

• The principle of justice requires that equals are treated equally, and non-equals are treated non-equally (e.g., how we treat an infant vs. an adult)

§46.111 Criteria for IRB approval of research.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.
Note:

• The Belmont Report was issued by a committee based solely in the United States
  o Individualism is #1!
• Consider ethical principles of other cultures
  o Value of complex relationships
  o Benefit to society/family overriding autonomy
  o Paternalism
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- **1979**: Belmont Report
- **1981**: Department of Health and Human Services (DHHS) and Food and Drug Administration (FDA) issue regulations based on the Belmont Report
- **1991**
A Brief History of Human Subjects Protection

1966
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Belmont Report

1981
Department of Health and Human Services (DHHS) and Food and Drug Administration (FDA) issue regulations based on the Belmont Report

1991
The Common Rule: the core DHHS regulations (45 CFR Part 46, Subpart A) were formally adopted by more than a dozen other Departments and Agencies that conduct or fund research
Research Ethics vs Research Regulation
Regulation vs. Guidance

**Regulation (Law)**
Federal/state requirements *must* be complied with

**Guidance (Ethics)**
Best practices recommended by the agency; optional

**Policy**
Institutional requirements *must* be complied with
# Research vs. Clinical Care

<table>
<thead>
<tr>
<th></th>
<th>Clinical Care</th>
<th>Research</th>
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<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>provide personal care for particular patients</td>
<td>generalizable knowledge</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>none</td>
<td>randomization, blinding, placebo controls, protocols restricting treatment flexibility, washout periods, and research procedures to measure study outcomes</td>
</tr>
<tr>
<td><strong>Justification of Risks</strong></td>
<td>potential medical benefits to patients</td>
<td>anticipated value of knowledge</td>
</tr>
<tr>
<td><strong>Relationship</strong></td>
<td>Fiduciary relationship with patient</td>
<td>Primary obligation to research</td>
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## What Regulations?

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<th>Organization</th>
<th>Regulation</th>
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<tr>
<td>OHRP</td>
<td><strong>Common Rule</strong> <em>(45 CFR §46)</em></td>
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<tr>
<td>FDA</td>
<td>Device, Drug and IRB regulations <em>(21 CFR §812; §312, §50, and §56)</em></td>
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<td>DoD</td>
<td>Instruction 3216.02</td>
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<td>Office of Civil Rights</td>
<td><strong>HIPAA</strong> <em>(45 CFR §160 and §164)</em></td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation (ICH) <strong>Good Clinical Practice</strong></td>
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<tr>
<td>EUGDPR</td>
<td>European Union General Data Protection Regulation</td>
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<tr>
<td>NIH</td>
<td>Imposes requirements on funded research</td>
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<td><strong>State, Local, and Institutional</strong> Regulations</td>
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Office of Human Research Protections (OHRP)

Depends on your FWA (Federalwide Assurance)

- Written documentation of an institution’s commitment to comply with federal regulations governing (federally supported) human subjects research
- Each legally separate entity must have its own FWA
  - Includes:
    - Statement of ethical principles
    - An assurance of compliance for all federally supported research
  - Technically only required for federally supported research
    - NY State Regulations – essentially require extension to all research
Common Rule
(45 CFR §46, Subpart A)

Requirements for:
• Assuring compliance by research institutions
• Researchers obtaining and documenting informed consent
• Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping

Additional protections for certain vulnerable research subjects (outside the Common Rule):
  o Pregnant women, fetuses, and neonates (Subpart B)
  o Prisoners (Subpart C)
  o Children (Subpart D)
At WCM/NYP

Apply the Common Rule to all research
Apply the additional protections for pregnant women, fetuses, neonates, and children to all research
Send prisoner research to an external IRB (BRANY) to review
Federal Drug Administration (FDA)

- **Title 21, Parts 50, 56, 312, 812**
- **Regulations for research involving FDA regulated drugs, devices, biologics**
  - New
  - Changing marketing or labeling
- **Data Safety Monitoring Board**
  - Required for all clinical trials
  - 5-10 experts review data every 6 to 12 months
  - Independent board
When Do FDA Regulations Apply?

- Clinical Investigation instead of research
- Test article, what’s that?
- Not your typical human subject…
FDA Exceptions for Obtaining Informed Consent

Life-threatening conditions that meet all of the following:

- Investigator and another physician believes the situation necessitates the use of a test article
- Subject or representative cannot consent
- Insufficient time to obtain consent
- No alternative available that provides and equal or better chance of survival
Differences between OHRP & FDA Regs

- FDA has not adopted the Common Rule
- Consult with your IRB analyst if you are unsure which ones apply

Health Information Portability and Accountability Act (HIPAA)

- Authorization to view protected health information (PHI) in medical records
- Authorization for disclosure of PHI ≠ Consent for research
- Waiver of authorization possible
- Are you a covered entity?
  - A health care provider who transmits any protected health information in connection with a transaction covered by HIPAA (claims, benefit eligibility inquiries, referral authorization requests, et al.)
    - HIPAA guidance: http://privacyruleandresearch.nih.gov/
  - Consider research conducted at *either* WCM or NYP to be under a covered entity
International Conference on Harmonisation (ICH)

Good Clinical Practice (GCP) is an international standard for the design, conduct, monitoring, and reporting of clinical research.

• FDA considers ICH-GCP to be guidance only
• Conducting research in a country regulated by ICH
• Conducting research under a contract that binds you to the ICH
General Data Protection Regulation (GDPR)

• European privacy law that regulates processing of all “personal data”

• When should you care?
  o Research taking place in the EU or using data from the EU
  o Research sponsored by an EU-based company
  o Are the subjects physically located in the EU (regardless of citizenship)?

• Very particular requirements for consent or “waiver” (more stringent than HIPAA)

https://gdpr.eu/
Is it over?
Could Tuskegee Happen Again?
Could HeLa?
Why we think it can…

• Are there other areas where treatment options are changing?
• Are there other areas where our understanding of the ethics are changing?
• To what extent is the concept of “ethical research” relative?
Evidence it has happened...
So, what keeps us honest?
In order to approve research involving human subjects, the IRB must determine the following requirements are satisfied:

- Risks to subjects are minimized by:
  1) Using procedures consistent with sound research design, using procedures already done on the subjects for other purposes, and;
  2) Without exposing subjects to unnecessary risk.

- Risk to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and of the importance of the knowledge that may be reasonably expected as a result.

- Selection of subjects is equitable.

- Additional safeguards have been included in the study to protect the rights and welfare of subjects who are vulnerable to coercion or undue influence.

- Informed consent will be appropriately documented or appropriately waived in accordance with §46.117(c).

- The research plan has adequate provision for monitoring the data collected to ensure subject safety.

- There are adequate provisions to protect the privacy of subjects.

- There are adequate provisions to maintain the confidentiality of data.

- The informed consent process is adequate.

- The documentation of informed consent is adequate.
Institutional Review Board (IRB)

*Headed by scientists/nonscientists in any institution/agency conducting research with human participants*

1. Minimization of risks to participants
2. Reasonable risk in relation to benefits
3. Equitable selection
4. Informed consent
5. Documentation of informed consent
6. Data monitoring
7. Privacy and confidentiality

IRB review is required for research involving human subjects
For More Information on the WCM IRB

Watch our IRB 101: An Introduction to the WCM IRB recording on METS page https://research.weill.cornell.edu/institutional-review-board/educational-resources/human-research-compliance-monthly-education-and

Educational Resources

Human Research Compliance Monthly Education and Training Series (HRC METS)

The Office of Human Research Compliance is pleased to offer a monthly education and training series for our stakeholders. The goal of this program is to provide a rotating series of sessions that will assist you in making sure your team receives the information they need to navigate the IRB process. If you missed our first session on IRB101: An Introduction to the WCM IRB, you can watch the video here (coming soon).

We hope you can join us for our next session:

Regulating Research: Ethics and the Responsible Conduct of Research

Thursday, September 15th, 2022