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

Office of Human Research Protection & Compliance
Melissa Epstein, PhD, MBE, CIP Executive Director

https://research.weill.cornell.edu
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

10 Points of The Nuremberg Code

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!)
10 Points of The Nuremberg Code, Cont.

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

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

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

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

- **STD Inoculation Study**
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  - Gonorrhea and syphilis injected into 696 subjects: Prisoners, mental patients, orphans
  - 1946-1948

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

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

- **The Stanford Prison Experiment**
  - How does playing a role change one’s behaviors?
  - 1971

A Brief History of Human Subjects Protection

- **Ethics and clinical research by Henry Beecher**
  - 1966

- **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

1974

1979

1981
National Research Act
- Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

1991

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1979
Belmont Report

1981

1991

Advisory Panel
Convened in 1972
The Belmont Report
Basic Ethical Principles

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, $46.119$.

(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

Justice

- Fairness in the distribution of the benefits and burdens of research
  - 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)
Note:

- The Belmont Report was issued by a committee based solely in the United States
  - Individualism is #1!
- Consider ethical principles of other cultures
  - Value of complex relationships
  - Benefit to society/family overriding autonomy
  - Paternalism

A Brief History of Human Subjects Protection

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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
A Brief History of Human Subjects Protection

- **1966**: Ethics and clinical research by Henry Beecher
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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**: 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

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Research Ethics vs Research Regulation

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

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<tr>
<th>Organization</th>
<th>Regulation</th>
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<tr>
<td>OHRP</td>
<td>Common Rule (45 CFR §46)</td>
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<tr>
<td>FDA</td>
<td>Device, Drug and IRB regulations (21 CFR §812; §312, §50, and §56)</td>
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<td>DoD</td>
<td>Instruction 3216.02</td>
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<td>Office of Civil Rights</td>
<td>HIPAA (45 CFR §160 and §164)</td>
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<td>ICH</td>
<td>International Conference on Harmonisation (ICH) Good Clinical Practice</td>
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<td>EUGDPR</td>
<td>European Union General Data Protection Regulation</td>
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<td>NIH</td>
<td>Imposes requirements on funded research</td>
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<td>State, Local, and Institutional 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):
- Pregnant women, fetuses, and neonates (Subpart B)
- Prisoners (Subpart C)
- 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)

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?
  - Research taking place in the EU or using data from the EU
  - Research sponsored by an EU-based company
  - 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/
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?

Approval Criteria (45 CFR 46.111 / 21 CFR 56.111)

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