

Welcome!

- The session will begin shortly; for those joining us via Zoom, please take a moment to make sure your microphone is muted
- This session will be recorded
- There will be a Q&A session after this presentation
- Please reserve your questions until then OR for those on Zoom put questions in the chat and we will address them after the presentation
- Not registered? Please register now using the QR code



Life After IRB Approval

Post-Approval Responsibilities and Procedures



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Alyssa Wheeler



7+ years of experience in human
research protections

Joined WCM in 2020

Margaret Mackenzie, MM



9+ years of experience in human research
protections

Joined WCM in 2014



Alicia Caldwell



5+ years of experience in human research protections

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6+ years of experience in human research
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Joined WCM in 2022



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Session Outline

- IRB Mandate
- Post-Approval Responsibilities
 - Research Team Responsibilities
 - IRB Responsibilities
- Post Approval Requirements and Processes
 - Amendments
 - Annual Reviews (CR/PAM-AR)
 - Reportable Events
 - Study Closures
- Q & A



IRB Mandate: Human Subjects Protections

Protect the rights, welfare, and privacy of human subjects in research

One of the primary roles of the IRB is to review, approve, and monitor research protocols to ensure they adhere to ethical standards and regulatory requirements (including federal, state, and institutional guidelines).

IRB purview is limited to research involving human subjects



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IRB Mandate: Human Subjects Protections



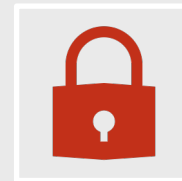
Basic Ethical Principles (The Belmont Report)

Respect for Persons
Beneficence
Justice



Federal Regulations

Common Rule [§46.111]
FDA
DOD
NIH
European Union GDPR
State and local laws



Institutional Policies

Conflict of Interest
Training and Education
Data use/transfer
Information and technology
security
Record keeping



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For a discussion on which regulations apply when,
please watch our METS from September 2023

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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/>

Post-Approval Responsibilities

IRB and Research Team Responsibilities



Research Team Responsibilities

Principal Investigator:

- Selection of qualified individuals for roles on study team.
- Complete knowledge of protocol, investigator's brochure(s), and consent form(s).
- Process for oversight of study team.
- Process for monitoring subject safety and data collection.
- Understanding of reporting obligations to funding sources, FDA (if applicable), and IRB.
- Understanding of scope of responsibility for multi-site studies, PI-initiated studies, federally funded studies.
- Understanding of federal, IRB, and institutional policies and regulations applicable to the research and conduct the research ethically.

Research Team

- Understanding of federal, IRB, and institutional regulations and policies applicable to the research.
- Appropriate knowledge (according to role) of the study's purpose(s), activities, risks, and benefits.
- Thorough understanding of the individual's role on the study and its relation to regulations and policies.
- Understanding of reporting obligations to the PI, IRB, and institution and conduct the research ethically.



IRB Responsibilities

- Post-approval oversight requires ongoing monitoring and review to ensure compliance with current regulations, guidelines and institutional policies and procedures [*§46.108(3), §46.109*]
- Post-approval review mechanisms include:
 - Amendments
 - Annual Reviews
 - Reportable Events

Post-Approval Requirements and Processes

Why, When, & What Is Required?



Amendments



Why and When Is an Amendment Required?

Why: Researchers are required to report to the IRB proposed changes in a research activity, and researchers must conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB.
[§46.108]

When: BEFORE implementing those changes, except those necessary to eliminate apparent immediate hazards to subjects

What Are the Amendment Types?

Extent of the proposed modifications

- Major changes
- Minor changes
- Administrative changes

WRG Submission Types

- Amendment
 - Major, minor, and most administrative changes
- Administrative Amendment
 - Specific limited administrative changes

Major vs. Minor vs. Administrative Changes

- Major
- Minor
- Administrative

Major vs. Minor vs. Administrative Changes

- Major – **substantial alterations** that could impact the IRB's previous determinations
- Minor
- Administrative

Major vs. Minor vs. Administrative Changes

- Major – **substantial alterations** that could impact the IRB's previous determinations
- Minor – **no substantial alterations**, unlikely to impact the IRB's previous determinations
- Administrative

Major vs. Minor vs. Administrative Changes

- Major – **substantial alterations** that could impact the IRB's previous determinations
- Minor – **no substantial alterations**, unlikely to impact the IRB's previous determinations
- Administrative – alterations that have no impact on the IRB's previous determinations

Determining Level of Review

- **Minor and administrative changes** undergo expedited, expedited-like, or exempt review
- **Major changes:**
 - If initially full board, continue to undergo full board review
 - If initially expedited/exempt, continue to undergo expedited/exempt review, unless alterations fall outside of initial review categories

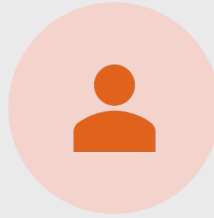
Remember: *Expedited* does not mean "FAST," it is a level of review



Previously-Approved Procedures and Requests for Modifications



RESEARCH
TEAM
REVISIONS



NEW REVIEWER



REGULATION
CHANGES



POLICY
CHANGES



Annual Reviews

Continuing Reviews (CRs)

Post-Approval Monitoring – Annual Reports (PAM-ARs)



Why Is a Continuing Review (CR) Required?



Regulations mandate that IRBs have procedures and a framework for periodically reviewing the conduct of research by investigators



Familiarity of research gained through these reviews does not relieve the IRB of the responsibility to conduct continuing review at least annually

When Is a Continuing Review (CR) Required?

Pre-2018 Common Rule - Initially approved before to January 21, 2019

- At least once per year or at intervals appropriate to the degree of risk, but no less than once per year.

2018 Revised Common Rule - Initially approved on or after January 21, 2019

- Studies reviewed via full board because they did not qualify for expedited review,
- Studies governed by other regulations (like those governed by the FDA)
- Studies for which it is required by the terms of a grant, contract, or other agreement;
- Studies involving topics, procedures, or data that may be considered sensitive;
- Studies involving vulnerable subjects or procedures that increase subjects' vulnerability

To determine whether the IRB has required a continuing review, refer to your approval letter



What Does the IRB Assess at Continuing Review?

- Confirm criteria for approval continue to be met, including but not limited to:
 - Risk to subjects are minimized
 - Informed consent process is appropriate for the study design, ethical, and compliant
- Additional review process involves:
 - Review approved documents for consistency and compliance
 - Evaluate the current progress and status of the study

Reminder to submit continuing review at least 60-days in advance of expiration and no activities are permitted after the study expires



Why and When Is a PAM-AR Required?

WHY: The regulations changed

- The 2018 Revised Common rule added flexibility to the requirements for annual review
- Such that, studies approved using expedited review procedures no longer require a continuing review, unless otherwise requested by the IRB

WHEN: Annually

- For minimal risk studies initially approved using expedited review procedures [§46.110] a Post Approval Monitoring – Annual Report (PAM-AR) is required

To determine whether the IRB has required a PAM-AR, refer to your approval letter



What Is the PAM-AR?

The PAM-AR is a check-in regarding

- Enrollment status
- Any unexpected issues that may necessitate further review
- Confirmation no activities have been conducted outside of IRB approval

Unlike a continuing review, PAM-AR

- Is not an IRB review nor a re-assessment of the criteria for approval
- Does not permit revisions (including personnel)
- Does not include a review of previously approved research materials nor stamping of materials
- Submit renewal within 30-days of the study's approval end date



Reportable Events



Why Are Reportable Events Required?

- *IRB Initial Review*
 - Informed **consent** accurately and appropriately **conveys known risks and benefits** [§46.111(4)]
 - Plan to **manage and mitigate these risks and monitor for new ones** (e.g., via DSMC, IMM, or PI/co-I review of AEs) [§46.111(a)(1) and §46.111(a)(6)]
- *Post-Approval Monitoring*
 - The research team can't initiate a change to the protocol **unless**:
 - It's approved by the IRB first; or
 - The change is necessary to eliminate an apparent immediate hazard to a subject [§46.108(a)(3)]
 - IRB policies must allow for prompt reporting (to IRB, Institutional Official/OHRP/FDA) of serious or continuing noncompliance and unanticipated problems [§46.108(a)(4)]



Why Are Reportable Events Required?

- **Unanticipated Problems (UPs)**
 - Unexpected (in nature, severity or frequency); **and**
 - At least possibly related to the procedures involved in the research; **and**
 - **Suggests increased** (physical, economic, psychological, or social) **risk** (even if no harm occurred); usually prompts amendment
- **Serious Noncompliance**
 - Noncompliant event that **substantively**:
 - Increases risk; **or**
 - Decreases safety/rights/welfare; **or**
 - Decreases potential benefits; **or**
 - Compromises integrity of study
- **Continuing Noncompliance**
 - **Pattern** of noncompliance indicating unwillingness to comply with, or lack of knowledge of regulations, policies or the protocol that:
 - May lead to adverse effect or increase risk or jeopardize study integrity



When and What: Reportable Event Types

- **Adverse Event**
- **Unplanned Protocol Deviation**
- **Planned Deviation**
(“exception request”)
- **Change Initiated to Eliminate an Apparent Immediate Hazard to a Subject**
- **Breach of Confidentiality**

Definition

Unexpected; at least possibly related; suggests research places subjects or others at greater risk of harm

Example

Mild liver injury is a known risk in ICF, but shortly after taking the study drug a subject experiences liver failure.

- Severity is unexpected
- Not attributable to subject’s underlying disease or risk factor profile.

Reporting Requirement

Report to IRB within 7 calendar days



When and What: Reportable Event Types

- **Adverse Event (cont'd)**
- **Unplanned Protocol Deviation**
- **Planned Deviation**
(“exception request”)
- **Change Initiated to Eliminate an Apparent Immediate Hazard to a Subject**
- **Breach of Confidentiality**

Additional Information

Generally, will warrant substantive protocol or consent changes or other measures to protect safety, rights, and welfare of participants:

- *Modification of eligibility criteria* to mitigate the newly identified risks
- Implementation of *additional procedures for monitoring* subjects
- *Modification of informed consent* documents to include a description of newly recognized risks

Note: Most AEs are not unanticipated problems.



When and What: Reportable Event Types

- Adverse Event
- **Unplanned Protocol Deviation**
- Planned Deviation (“exception request”)
- Change Initiated to Eliminate an Apparent Immediate Hazard to a Subject
- Breach of Confidentiality

Definition

- Deviation has the potential to negatively impact subject safety or integrity of study data, or affect the subject’s willingness to participate; **AND**
- Places subjects at greater risk of harm (including psychological, economic or social harm)

Example

Missed safety labs.

Reporting Requirement

Report to IRB within 7 calendar days and add to deviation log.

Additional Information

May be called "protocol violation" or "major deviation" by sponsor.



When and What: Reportable Event Types

- Adverse Event
- **Unplanned Protocol Deviation (cont'd)**
- Planned Deviation (“exception request”)
- Change Initiated to Eliminate an Apparent Immediate Hazard to a Subject
- Breach of Confidentiality

Definition

Any deviation not otherwise promptly reportable, but that occurs repeatedly.

Example

Labs missed repeatedly.

Reporting Requirement

Report to IRB within 7 calendar days and add to deviation log.

Additional Information

Repeatedly=3 times or more



When and What: Reportable Event Types

- Adverse Event
- Unplanned Protocol Deviation
- **Planned Deviation**
(“exception request”)
- Change Initiated to Eliminate an Apparent Immediate Hazard to a Subject
- Breach of Confidentiality

Definition

Intentional one-time change from the protocol for which IRB approval is required.

Example

Enrolling subject who doesn't meet the inclusion criteria.

Reporting Requirement

Submit to IRB for approval prior to initiation. Add to deviation log.

Additional Information

If PI repeatedly requests approval to enroll subjects who don't meet inclusion criteria, it is an indication the inclusion criteria should be amended.



When and What: Reportable Event Types

- Adverse Event
- Unplanned Protocol Deviation
- Planned Deviation (“exception request”)
- **Change Initiated to Eliminate an Apparent Immediate Hazard to a Subject**
- Breach of Confidentiality

Definition

Intentional change from the IRB-approved protocol to eliminate an apparent immediate hazard.

Example

Immediate reduction or discontinuation of the study drug dose based on new toxicity information from an interim DSMC review

Reporting Requirement

Report to IRB within 24 hours.

Additional Information

- Considered by OHRP to be an indication that an Unanticipated Problem has occurred.
- Requires prompt reporting to the FDA via amendment submission.



When and What: Reportable Event Types

- Adverse Event
- Unplanned Protocol Deviation
- Planned Deviation (“exception request”)
- Change Initiated to Eliminate an Apparent Immediate Hazard to a Subject
- **Breach of Confidentiality**

Definition

Any accidental disclosure of PHI/identifiable private information

Example

Emailing PHI to an unintended recipient.

Reporting Requirement

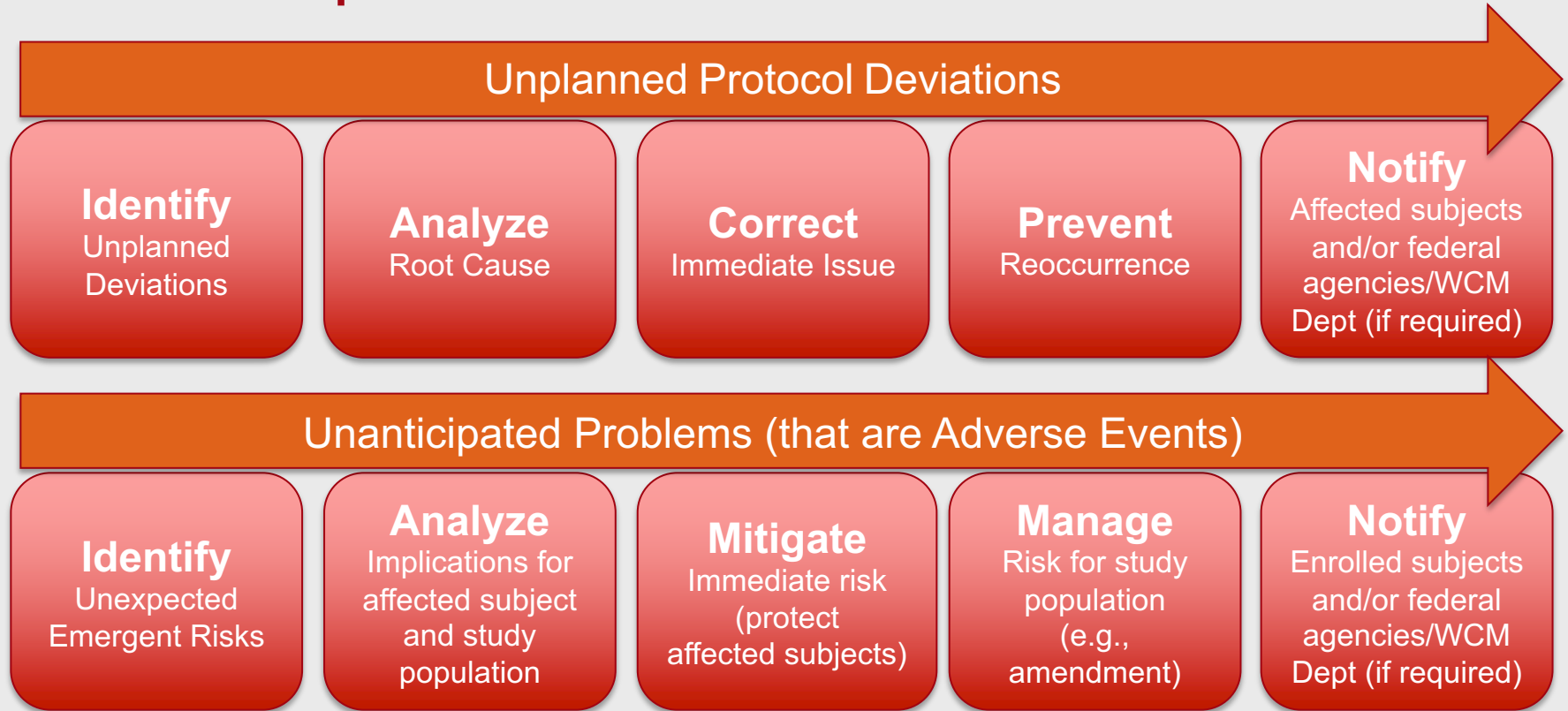
Report to IRB within 24 hours.

Additional Information

IRB review occurs concurrent with the Privacy Office (privacy@med.cornell.edu)



What: Report Content & Review Process



Study Closures



Why Is a Closure Report Required?

The IRB responsibilities are limited to the oversight of research involving Human Subjects [*§46.111 / 21 CFR 56.111*]

Once a research study has progressed to a stage that **no longer involves human subjects**, the study can be closed as IRB oversight is no longer required

When Is a Closure Report Required?

The PI is responsible for closing out an IRB approved project if any of the following conditions exist:

1. All research/clinical investigation activities including analysis of identifiable data are complete;
2. The research study was never initiated;
3. Participant enrollment and data collection is complete, and the only remaining activity is analysis of de-identified data and there are no identifying links or codes to the de-identified data;
4. The PI plans to leave WCM and/or intends to continue the research activities at another institution.

The PI cannot close out an active IRB approved project if:

1. There is still long-term follow-up of participants or collection of identifiable data.
2. Analyzing identifiable data (including data with codes or links to identifiers).
3. Biological specimens containing Personally Identifiable Information (PII) is being maintained in a repository



What Are the Closure Report Procedures?

Confirm:

- Participant enrollment is complete
- Data collection is complete
- Only data analysis, as approved in the protocol, of already collected data remains, if applicable
- Data are de-identified (e.g., link to participant identifiers has been destroyed audio recording transcribed with pseudonyms then destroyed, etc.)

Review:

- Summary of findings
- Any changes since the last annual review



Helpful Resources

Guidance Documents:

- [Amending an Existing Protocol vs. Submitting a New One](#)
- [Lapses in IRB Approval: Continuing Reviews and PAM-AR](#)
- [Protocol Deviations](#)

Standard Operating Policies:

- [Review of Research subject to the 2018 Common Rule](#)
- [Changes to Approved Research](#)
- [Continuing Review](#)
- [Reportable Events/Immediate Reporting](#)
- [Study Closure](#)

Monthly Education and Training Series (METS)



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Guidelines



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Questions & Answers



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Scan the QR code to
request a consult
during our on-site
Tuesday, 1/9 through
Thursday 1/11



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