IRB Submissions
Approvals, Deferrals &
Everything In-Between

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Role of the IRB

• It is within the authority of the IRB to review research projects involving human subjects and approve them if the rights and welfare of research subjects are protected.

• In doing so the IRB must ensure that the human subject research is conducted ethically and in compliance with Federal, state and local law, as well as any institutional policies and procedures.
Ethical Principles Governing Human Research

• The Belmont Report summarizes the basic ethical principles identified by the Commission for the Protection of Human Subjects in Biomedical and Behavioral Research to assist in resolving the ethical dilemmas that surround the conduct of research.

  – Respect for Persons – Addresses the autonomy of individuals and the importance of the consent process
  – Beneficence – Protect from harm by assessing risks and benefits
  – Justice – Treat people fairly; equally share the benefits/burdens of research
The Belmont Report and the ethical principles contained within it derive the regulatory criteria for approval of research involving humans.

The Office of Human Research Protections (OHRP), within the US Department of Health and Human Services (DHHS), oversees the adherence to these regulations found in the Code of Federal Regulations, 45 CFR § 46.

Food and Drug Administration (FDA) regulated research has additional regulations which can be found in 21 CFR parts 50 and 56.

Also need to consider Office of Civil Rights (OCR) for HIPAA regulations, Department of Defense/Justice (DoD, DoJ), etc.

Federal Wide Assurance
Definition of FWA

• Federal Wide Assurance

• An FWA is an institutional assurance of protection for human subjects.

• Written documentation of an institution’s commitment to comply with the federal regulations governing human subjects research.

• An FWA must be obtained by every institution conducting federally funded human subjects research.
45 CFR 46, Subpart A
(Common Rule)

• Protective Mechanisms Established by the Common Rule
  – 19 Federal Agencies adopted the common rule, based on 45CFR46 Subpart A (FDA did not adopt the common rule)
  – Review of research by an IRB
  – Informed consent of subjects
  – Institutional assurances of compliance
  – Additional protections for Pregnant women, Human Fetuses and Neonates (Subpart B), Prisoners (Subpart C) and Minors (Subpart D)
45 CFR 46
(Common Rule)

Criteria for IRB review

*Research* means a systematic investigation, including research development, testing, and evaluation designed to develop or contribute to generalizable knowledge.
A *Human subject* is a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information- anything you might learn about any part of any living person counts as obtaining information.
FDA Regulations

• A Clinical investigation is any experiment that involves a test article and one or more human subjects

• A Human subject is an individual who is, or becomes, a participant in research either as a recipient of a test article or as a control. A subject may be either a healthy individual or a patient.

• A Test article is any drug (including biological products for human use), medical device for human use, human food additive, color additive, electronic product.
45 CFR 46 and 21 CFR 50,51

- Govern the make-up of the IRB
  - Shall have at least 5 members.
  - Must have varying backgrounds.
  - At least one member whose primary concern is scientific.
  - At least one member whose primary concern is in non-scientific areas.
  - At least one member who is not affiliated with the institution.

Members may not participate in the IRB review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.
Information about WCMC IRBs

• 5 Boards
  – 2 General IRBs – Each meets twice a month
  – 2 Cancer IRBS – Each meets twice a month
  – 1 Expedited IRB – Assigned submissions weekly, meets on a quarterly basis

• 5 Chairs, with at least one Vice-Chair
• Scientists, non-scientists and community members
Criteria for Approval of Research
Approval criteria apply at all stages of review:

• Initial review
• Continuing review of research, including adverse events, deviations and non-compliance
• Review of amendments
• Review by a convened IRB
• Review by the expedited process
What do Board members need to consider during their review (45CFR § 46.111(a))?

- 45CFR § 46.111 (a)(1) – Minimization of risks
- 45CFR § 46.111 (a)(2) – Risk/Benefit ratio
- 45CFR § 46.111 (a)(3) – Equitable selection of subjects
- 45CFR § 46.111 (a)(4)/116 – Consent process
- 45CFR § 46.111 (a)(5)/117 – Consent documentation
- 45CFR § 46.111 (a)(6) – Data monitoring
- 45CFR § 46.111 (a)(7) – Privacy/confidentiality
- 45CFR § 46.111 (b) – Vulnerable subjects
What does the IRB look for to determine if the risks are minimized?

• Study design
• Compare standard of care for subject population to the experimental intervention
• Review of previous animal studies and literature on the research topic
• Data from previous clinical trials
• What Adverse Events would cause a subject to be removed from the study
• Stopping rules
• Data and Safety Monitoring Board (DSMB)
45CFR § 46.111 (a)(2) – Risk/Benefit Relationship

Must determine what is reasonable
• Subject population
• Alternative treatment

Risks to subjects
Anticipated benefits to subjects
Importance of knowledge expected to result
45CFR § 46.111 (a)(3) – Equitable subject selection

• Risks (burdens) and benefits should be fairly distributed
• Exclusion/inclusion criteria are clearly outlined
• Recruitment procedures are fair and not biased
Data Safety Monitoring Plan

- Who reviews data? Internal/External Monitor? Data Safety Monitoring Board?
- What data will be reviewed?
- When will data be reviewed? At what intervals will data be reviewed?
- What will be done with the information resulting from the data? What are the stopping rules?
Informed consent

- 45CFR § 46.111 (a)(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.

- 45CFR § 46.111 (a)(4) - Informed consent will be appropriately documented, in accordance with, and to the extent required by § 46.117.
45CFR § 46.116

- Defines General Requirements of Informed consent
- Defines criteria by which an IRB may approve a consent procedure which excludes or alters some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents
45CFR § 46.111 (a)(7) – Privacy/Confidentiality

- Privacy refers to persons and their interest in controlling access to themselves
  - Is the use of identifiers or links to identifiers necessary to reach study endpoints?
- Confidentiality refers to agreements with the participant about how data are to be maintained.
  - Are there adequate plans to store and code the data?
SUBMISSION TYPES
Types of Submissions

• Initial Application – proposed research that has never been reviewed by the IRB
• Amendment – any change to currently approved research
• Continuing Review – annual protocol renewal
• Response to Questions
  – “Modifications Required” disposition letter
  – “Deferred” disposition letter
Types of Submissions (cont.)

• Acknowledgment – no change to any IRB related documents, including application, consent, ads, etc.

• Immediate Report – protocol deviations and adverse events that fit the immediate reporting policy

• Protocol Exception – one time planned deviation requests submitted and approved by the IRB prior to completion
IRB Submission Process
CSEC Workflow

1. Complete CSEC Submission Part A
2. Receive Email with Link to CSEC Submission Part B and IRB Protocol number from CSEC administrator.
3. Exempt protocols and general (non-cancer) protocols utilizing the CTSC will receive an email indicting they are exempt from CSEC review
4. In parallel, complete CSEC Submission Part B along with the eIRB application.
5. Submit CSEC Submission Part B.
6. Receive CSEC disposition and respond accordingly.
7. Upon approval, CSEC will upload approval letter and complete the eIRB application.
8. Submit eIRB protocol application.
IRB Workflow

• After approval by the CSEC, and the submission is ready, the PI submits
• All submissions default to “Initial submission, full board review”
• Initial submissions must be approved by the Department Chair before they are routed to the IRB office (should be done within 3 days of receiving the e-mail notification)
• Continuing reviews and amendments are routed directly to the IRB office
IRB Workflow (Continued)

• Once routed to the IRB office, the Assistant Director (Milda) or Director (Rosemary) of HRPP reviews the submission to determine the level of IRB review (Expedited or full board) and designates the submission as an initial, amendment, continuing review or response to previous IRB notification (Response to questions; RTQ)

• The submission is then assigned to the appropriate IRB administrator
How are Submissions Assigned?

- All cancer-related submissions (either expedited or full board) will be assigned to one of the two cancer-focused IRBs
- All general submissions requiring convened IRB review will be assigned to one of the two general IRBs
- All general expedited submissions will be assigned to the expedited IRB
- FB submissions assigned one week prior to meeting
- Expedited Submissions assigned weekly to Expedited IRB
IRB workflow (Continued)

• For full board and expedited submissions, no deadline
• The agenda for a meeting closes one week prior to the meeting date
• Once it is assigned to the IRB administrator, they should conduct the pre-review within 24-48 hours
• The protocol is either approved for review, or sent back to the PI for additional changes
• Once the submission is ready for review, it is assigned to the next available meeting
• Issue letters from convened meetings are sent within 24-48 hours of the meeting
Purpose of the Pre-Review

- Purpose of the pre-review is to ensure that the IRB submission is ready to be reviewed
  - Look for discrepancies in the application
  - Make sure all the required documentation is present
Reasons for Return on a Pre-Review

• Text boxes only says “See attached”. Need some information, in particular in the Study design.

• Attached documents not adequately labeled

• Inconsistencies throughout the protocol (answer in one section does not match an answer in another section).

• For RTQ, point-by-point response memo is either not attached or is not adequate.

• Continuing review-the accrual numbers do not correlate with the accrual numbers from the previous year

• Amendments-Insufficient justification
Review Types
Designation of review type depends on risk level of the study - Minimal Risk or Greater than Minimal Risk

“A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(i)).”
• Exempt Review – Minimal Risk and fits into specific categories
• Expedited Review – Minimal Risk and fits into specific categories
• Facilitated Review – Review of research conducted under the Cooperative Agreement WCMC has with several institutions (MSKCC, Rockefeller, Cornell-Ithaca, Columbia, Rogosin Institute, HSS) and Central IRBs (CIRB, NeuroNEXT, StrokeNet)
• Full Board Review – Typically Greater than Minimal Risk studies, often involving FDA-regulated products; Minimal risk studies that do not qualify for expedited review under category 1-7.
EXPEDITED REVIEW OF PROTOCOLS
In order to qualify for expedited review...

- Must meet two criteria as per 45CFR46.110:
  - Present no more than minimal risk to the subject and
  - Fit into one of 9 categories that are eligible for expedited review
    (45CFR46.110 [can be found at http://www.hhs.gov/ohrp/policy/expedited98.html])

- Amendments – no change to the risk of the study
- Besides blood collection amounts, there is no difference in the application of expedited IRB procedures between research involving adults and research involving children.
- Submissions are reviewed outside of a convened IRB meeting.
- Initial submissions that are minimal risk but do not fit categories 1-7 must be reviewed at a convened meeting
Review by the Expedited IRB

- All submissions that qualify for expedited review are assigned to the expedited meetings.
- These meetings are scheduled on a weekly basis (every Thursday) and the submissions are assigned for review one week prior to the meeting date.
- These are not in-person meetings. Reviewers are requested to submit their reviews by the meeting date.
IRB Determinations

- Approved – all approval criteria are confirmed
- Approved Pending – administrative issues outstanding (e.g. contract execution, HRBAF, etc.)
- Modifications Required – directed/minor changes – expedited re-review by original reviewers allowed
- Deferred – substantial changes – requires re-review by original reviewers at convened IRB meeting
- Tabled – review could not be completed, added to next available agenda
- Disapproved – approval criteria can never be confirmed
  - Expedited Board cannot disapprove a study being reviewed under expedited procedures
What Happens After the Meeting

• Staff meets to go over the dispositions of the submissions
• Disposition letters are prepared by the staff
  – Review guides
  – Issues from the meeting that weren’t included in the review guides
  – Administrative issues uncovered during the pre-review
• Letters are sent within 24-48 hours after the meeting
• Researchers are given 60 days to respond back to the issues
• Expedited reviews – issues letter are sent within 24-48 hours of the administrator receiving the review.
Review of Modifications Required Responses

- Modification required responses: The IRB staff will review those that are truly directed.
- Any that require an assessment of the response are assigned to the original reviewer (if available).
- Once the administrator determines that the response is adequate (i.e., all the issues have been addressed), the response is immediately assigned.
- Non-staff IRB members are given 5 business days to submit their reviews.
- Additional issues may be raised as a result of the response.
Review of Deferral Responses

• Deferral responses are processed by the original IRB administrator
• Deferral responses are assigned to the original reviewers and are scheduled to be discussed by the same board that performed the original review
• Exceptions can be made upon request
Analysis of common issues identified at IRB review

- Non-Technical Research Plan is technical (copied/pasted) from elsewhere
- Non-technical plan is insufficient (The study design should include information about the hypothesis, research question, study procedures vs. experimental procedures, etc.)
- Data acquisition sheet for chart reviews (important for exemption requests)
- Incomplete Monitoring plans and risks assessment
- Informed consent document is technical
- Procedures and risks of the study and alternative options (standard of care) not clearly outlined
- Recruitment plan unclear
- Inclusion/exclusion criteria unclear
- Failure to document agreement to participate (and related capabilities) of other departments and investigators
Analysis of common issues identified at IRB review (Cont.)

- Inconsistencies between IRB application and protocol documents
- Inadequate statistical plan
- Unclear what is being billed to study vs subject/insurance
- Confidentiality issues
Common Mistakes – Amendments

• Not describing the amendment and the rationale for it
• Copying/pasting from the sponsor’s documents
• Not addressing changes in risk and/or benefit as a result of the amendment
• If adding an investigator, not submitting a revised HRBAF (may be changing)
Common Mistakes– Continuing Review

• No preliminary data and no justification
• Indicate that AEs have been reported since the last continuing review, then forget to submit the AE table.
• Indicate that there is a DSMB, then forget to submit the DSMB report.
• More subjects were recruited than was originally requested when the protocol was approved.
• Discrepancy in the number of subjects recruited when compared to the previous CR.
Helpful Suggestions for using eIRB

- eIRB training guide
- To access eIRB outside the secure network, must use either webVPN or VPN client.
- Recommended browser is Firefox.
- When emailing/calling IRB office, having the full submission number is very helpful.
- Delete a submission using the delete option under Protocol Options….
  - NOTE: deleting CRs/Amendments mid-submission will erase all of the information entered in additional forms.
Helpful Suggestions (cont.)

• Any conflicts related questions should go to conflicts@med.cornell.edu.

• Research Coordinator can check if submission is complete before sending to PI by clicking “Submit for Review.” Any missing information will come up and if it’s all complete, you can send a notification to the PI that the submission is ready.

• The assigned IRB contact should be your “go-to” person for the specific submission
  – Any questions related to the submission should be directed to your contact via the Comment feature in the protocol.
Helpful Suggestions (cont.)

• Once a CR or Amendment are approved, the R### and A### are removed and the fully approved protocol can be found under “All Active Protocols.”
Important Websites

- Main WCMC IRB Website
  - http://researchintegrity.weill.cornell.edu/institutional_review_board/index.html
- IRB Forms Page
  - http://researchintegrity.weill.cornell.edu/institutional_review_board/forms.html
- HIPAA in Research Forms
  - http://researchintegrity.weill.cornell.edu/HIPAA_in_research/hippa_forms.html
- FAQ Page
  - http://researchintegrity.weill.cornell.edu/institutional_review_board/irb_faq_new.html
- Meeting Schedule
  - http://researchintegrity.weill.cornell.edu/institutional_review_board/irbschedule.html
General Contact information

- IRB list-serve: irb@med.cornell.edu
  - General questions regarding submissions
  - Technical issues with eIRB
  - Requesting access to a protocol
  - Request to add investigator to the system
  - Requesting closure of a protocol
  - Submission of Immediate reports
• For questions regarding the CSEC process or review
  GeneralCSEC@med.cornell.edu
  CancerCSEC@med.cornell.edu
Contact information

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