Submitting Continuing Reviews and/or Amendments to the IRB

Tufts-New England Medical Center
Tufts University Health Sciences

IRB Education Series
2006

Presentation may only be reused or reprinted with written permission from the Tufts-New England Medical Center/Tufts University IRB office.
What is continuing review...

• Periodic review of research previously approved by the IRB

• According to federal law the IRB must conduct continuing review “…at intervals appropriate to the degree of risk, but not less than once per year…” (45 CFR 46.109(e))

• Also according to federal law the IRB may “…observe or have third party observe the consent process and the research.” (45 CFR 46.109(e))
...and why is it important?

- On going assessment of the research:
  - Subject safety
  - Compliance with the protocol
  - Update of adverse events
- Propose amendments
- Revise and update study documents
Regulatory Interpretation Issued by the Government

• “The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. . . .”

Source: OHRP Compliance Activities: Common Findings and Guidance – 9/1/2000 (Compliance Oversight Branch Division of Human Subjects Protection, OHRP)

• “Please note that when continuing review does not occur by the date specified by the IRB, IRB approval expires automatically.” [emphasis in original]

Source: Letter to the University of Oklahoma Health Sciences Center, Michael Carome, M.D., OHRP Director, Division of Compliance Oversight in a letter dated October 19, 2000.
What does the IRB Consider at CR?

- Review is expected to be as rigorous as initial review
- Application of the Belmont Report
  - **Respect for Persons**
    - Informed consent
    - Voluntary participation
    - Freedom to withdraw from a study without penalty
    - Protect privacy and confidentiality
  - **Beneficence**
    - Risks are minimized
    - Benefits are maximized
    - Risks are justified by potential benefits
    - Conflicts of interest are managed or eliminated
  - **Justice**
    - Protection of vulnerable populations
    - Those who may benefit are not excluded
Type of Review: Expedited or Full

- Studies initially granted expedited approval may qualify for expedited CR if there have been no changes to the research.
- Studies initially approved by full IRB review may be expedited if:
  - The research is permanently closed to the enrollment of new subjects;
  - All subjects have completed all research related interventions; and;
  - The research remains active only for long-term follow-up of subjects;
  - No subjects have been enrolled and no additional risks have been identified;
  - The remaining research activities are limited to data analysis;
  - The IRB determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.
Expedited or Full: How Is It Decided?

- Determined in IRB office, based on:
  - Federal guidance
  - Discretion of reviewer
- IRB office will process based on above.
Continuing Review Applications if the Study is *Open to Enrollment (Full IRB Review)*

- Form V
- Protocol – current version
- ICF(s) – version used over the past year, current copy
- Education requirements satisfied
- Advertisement(s)
- Questionnaire(s)
- Form II (drug/compound)
- Form III (device)
- Form IV (research radiation)
- Form VI (tissue-banking)
- Optional TB ICF
- HIPAA documentation
• “Submit an original and TWO (2) copies of all documentation (protocol, ICF(s), Forms II, III, IV, VI, as applicable, and all necessary supporting documentation) to the IRB office, Box 817. Please ensure that at least one set of copies is single-sided. If you wish to terminate a study (or close a completed study) because no further work will be done or if the study was never initiated please submit a Termination letter. This, and all forms submitted to the IRB office, should be typed.”

• http://www.tufts.edu/central/research/msword/IRB/FormV%20ver%202014.doc
FORM V

D. Mandatory Human Subject Protection Education

- Especially important if new research team members have been added (remember to revise other documents: protocol, ICF, etc.)

- The completion of the education modules is mandatory for each research team member.

- Research Team Members: Those who are responsible for the design, conduct, or reporting of this research, such as the Principal and Co-Investigators, Research Nurses and Coordinators, Project Managers, etc.

- Based on an individual’s role (e.g., Co-I, coordinator)

- Education requirements and modules are accessible at: http://www.tufts.edu/central/research/IRB.htm#req
Education Modules

- OHRP *Investigator 101*

- Barnes lectures
  - September lecture, *Research Compliance: Basic Requirements and Accurate Record Keeping*
  - October lecture, *Recognizing and Reporting Adverse Events During a Clinical Trial*
  - December lecture, *What Researchers need to Know about Investigational Drugs and Devices under FDA Regulations (INDs/IDEs)*
F. Subject Population

- Do you wish to request additional subjects: Yes No
  If yes: submit a revised protocol.

- Number of subjects enrolled since the last continuing review (if applicable):

- Total number of subjects enrolled to date (since study initiated):

- In the past year, have any subjects withdrawn their participation from the study? Yes No
  Briefly state the reason.

- In the past year, have any subjects been withdrawn by the PI or Sponsor? Yes No
  Briefly state the reason.

- Number of subjects that are being followed (if applicable):
FORM V

J. Status Report:

• Has this research changed in any way since the last continuing review? Yes  No

  If “Yes,” itemize the changes that have been approved.

• Are there revisions or changes that are being submitted with this application? Yes  No

Please attach a summary of any amendments, revisions, modifications to the research since the last review; any relevant multi-trial reports, any relevant recent literature, interim findings, or any other relevant information associated with the research.
FORM V

K. Serious Adverse or Unanticipated Events

• Have there been any **serious** adverse events or **unanticipated** events at Tufts-NEMC/TUHS?  Yes  No

*If “yes, attach a spread sheet or chart and address the events by itemizing all serious adverse events or unanticipated events that have occurred involving this research protocol since the initial review or the most recent continuing review.*

• Does this research study have a Data and Safety Monitoring Board?  Yes  No

*If “yes,” attach the most recent DSMB report (if available).*
Advertisements and Questionnaires

• All ads, questionnaires, pamphlets, summaries, etc., must be reviewed and approved by the IRB at CR

• All documents approved for use will be validated (stamped).
FORM II

• For any drug, substance, or biologic administered as part of the research.
• Don’t leave ANY blank fields – “N/A”
• Need the:
  • Investigator’s Brochure
  • Package insert information – don’t send the actual insert!
  • Micromedex® printout
  • MSDS sheets
• Reason for submission: updates, new information, etc.
• http://www.nemc.org/resadmin/Forms/HIRC/form2.doc
FORM III

- For any device used as part of the research.
- Don’t leave ANY blank fields – “N/A”
- If there is FDA correspondence/documentation, submit a copy
- Need the:
  - Investigator’s Brochure
  - Operator's Manual
  - User’s Guide
- Reason for submission: updates, new information, etc.
FORM IV

• For any radiation exposure as part of the research.
  • X-ray
  • CT scan
  • Fluoroscopy
  • PET scan
  • Nuclear medicine scan
• Only needs to be submitted if there has been a change in research-related radiation exposure since last approval by the Radiation Safety Officer (RSO).
• If there hasn’t been a change in research-related exposure, submit a cover letter signed by the Principal Investigator stating such and a copy of the last RSO signed Form IV.
• If a revised form is submitted it must be signed by the Radiation Safety Officer
• http://www.nemc.org/resadmin/Forms/HIRC/form4.doc
FORM VI

• For any sample banking

• Submit a copy of the tissue bank's written policies

• A copy of the optional tissue banking ICF
  • version used over the last year
  • version to be validated

• http://www.tufts.edu/central/research/msword/IRB/FormVI.doc
HIPAA Documentation

• Copy of the RAF or a letter signed by the PI that there have been no changes

• If a waiver was previously granted and
  • < 50 records reviewed, etc: names
  • > 50 records reviewed, etc: profile
  • Submit names/profile to the HIPAA Privacy Officer for Research
    • Jeffrey Weinstein (Tufts-NEMC)
    • XXX (TUSDM)
If the Research is *Closed to Enrollment*  
* (Original and 2 copies)

- Form V
- Protocol
- ICF(s) – if anyone was enrolled in the past year
- Education requirements satisfied
- Questionnaire(s), or any other document(s) still being administered/used
Submitted:

- Reviewed for:

  ✓ Completeness
  ✓ Education requirements
  ✓ Conflict of Interest Info

  ✓ Accordance with federal and state regulations and institutional policies
Reviewed by the Full IRB

Assigned to an IRB agenda
Reviewer Assigned

Reviewed at a convened IRB meeting

IRB letter sent to PI within 2 weeks of the meeting if changes/clarifications are needed

Approval letter is generated, signed, and sent to the PI.
Principal Investigator responds to IRB review requests for clarification/change:

Submission is reviewed by “expedited review procedures” unless it’s stipulated that it must return to the convened IRB

If necessary, additional information, *etc.*, is requested from the PI.

Approval letter is generated, signed, and sent to the PI. IRB members are notified.
What If IRB Approval Lapses?

• Don’t let it happen!
  • Courtesy reminders are sent to the Principal Investigator
• If CR doesn't take place and IRB approval lapses, the research must stop – all aspects (including follow-up and data analysis)
• The IRB will assess the medical interests of individual subjects and may determine interventions or interactions can continue (very limited circumstances).
• Enrollment of new subjects cannot occur after the expiration of IRB approval.
Amendments…At Continuing Review

- “Kills 2 birds with 1 stone”
- Submit tracked and untracked copies of all documents
- Submit a detailed letter signed by the PI
  - Explain rationale/need for changes
    - New safety information
    - Additional (or deleted) procedures
  - Explain who initiated changes
    - PI?
    - Sponsor?
Continuing Review Common Problems

- Incomplete submission – missing copies/documents
- ICF too technical or missing elements
- Required documents not provided
- Forms not complete or inaccurate/conflicting info on forms
- Signature of PI not provided
- Education requirements are not satisfied
- COI information is missing
Helpful Tips When Submitting Continuing Reviews

- Re-review ICF prior to submission
- Write ICF at an 8\textsuperscript{th} grade reading level.
- Address all issues if changes/clarifications are requested
- PI signatures present as required.
- If applicable, provide a copy of the grant.
- Provide requisite supporting documentation.
- Provide tracked and untracked copies of revised documents.
- Ensure all documents have a version date or number.
- Ensure education requirements are satisfied.
- Re-read information entered on the forms
Amendments Between Reviews

- Submit a detailed letter **signed by the PI**
  - Explain rationale/need for changes
    - New safety information – SAE
    - Additional (or deleted) procedures
    - DSMB report/interim analysis
  
- Explain who initiated changes
  - PI?
  - Sponsor?

- Submit tracked and untracked copies of all documents
Things to Consider When Submitting Amendments

• Do study documents need to be revised?
  • Protocol
  • ICF
  • Advertisements

• Which, if any, subjects does the amendment effect?
  • Prospective/new subjects
  • Those already enrolled and actively receiving intervention
  • Those enrolled in the study no longer receiving intervention but still being followed?
    • Detail the plan for notifying subjects
    • Will everyone re-consent?
Common Problems With Amendments

• Incomplete submission
  • Cover letter only – revised protocol not provided
  • Documents requiring revision (ICF, ads, questionnaires) not submitted
• Revised documents are too technical
• Signature of PI not provided
• Required documents not provided
More Information

- **OHRP**: http://www.hhs.gov/ohrp/
  - Guidance on Continuing Review (copy provided)
  - Code of Federal Regulations
    - http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
  - ICF Tips
    - http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm

- **FDA**: http://www.fda.gov/default.htm
  - http://www.fda.gov/oc/ohrt/irbs/review.html
    - http://www.irbforum.org/
IRB Leadership

- **IRB Chair:** David P. Chelmow, MD
- **IRB Vice-Chairs:** Edward L. Decker, PharmD
  
  Judith A. Frazier, RN, MEd
  
  Nicholas G. Guerina, MD, PhD

- **IRB Members** are from more than 17 divisions at Tufts-NEMC and Tufts University, including TUSM, TUSDM, HNRCA, etc., and community representatives who are not affiliated with either institution.
IRB office

• IRB Admin. and Operations Manager: Jennifer A. Graf
• IRB Coordinators: Julie Morelli Novak (IRB-RED)
  Elizabeth Kervis (IRB-BLUE)
• Continuing Review Coordinators: André Briola
  TBA
• Assistant IRB Coordinator: Kelly J. Shipman
• Administrative Assistant: Jennifer C. Coes
IRB Office
Box 817
(617) 636-7512

http://www.tufts.edu/central/research/IRB.htm