Issue in IRB Approvals:

What are the obligations of investigators and the IRB in maintaining IRB approval?
What are the consequences of a lapse in IRB approval?
How does the IRB evaluate lapses in approval?

Sponsored Projects Training/Educational Events
Brown Bag Session
January 31, 2013

Jan L. Hewett, B.S.N., J.D.
Roadmap

1. Institutional Review Board (IRB) – what is it?
2. IRB annual review and approval – what are the regulations?
3. What do the regulations require of the researcher?
4. What happens if you don’t follow the regulations?
What is an Institutional Review Board?
IRB

- Independent administrative body established to protect the rights and welfare of human research subjects”
- Ethical Review Board
- Mandated by the government
- Minimum of 5 members with varying backgrounds
- Must have scientific members, non-scientific members and non-affiliated member (community)
Yale University – Institutional Review Boards

YSM - Human Investigation Committees (HIC I - Oncology, II, III, IV)

FAS – Human Subject Committee
General IRB (HSC/HIC) Numbers

- 5 Boards
  - 1 meeting per week (weeks 1, 2 & 4)
  - 2 meetings per week (week 3)
- 4 Chairs
- 3 Vice-Chairs
- ~ 76 members
- ~ 15 staff (FTEs & Temps)
- ~ 3000 Principal Investigators
- ~ 6000 study coordinators
- ~ 7200 submissions per year
- ~ 2800 (full/expedited) & ~ 3200 (exemptions) active projects on file
IRB Office

• 5 Regulatory teams –
  – Senior Regulatory Analysts – pre-review all project applications and submissions
  – Each team have 1.5 individuals to assist with these applications and submissions
What does an IRB do?

Investigator Submits New Protocol (paper/electronically)

IRB Staff Pre-Review

- Minimal risk? Expeditable? Exempt?
  - IRB Chair or Member Review
    - Contingencies Requested
- Greater than Minimal Risk?
  - Full Convened Board Review
    - BAD
    - Contingencies Requested
  - IRB Staff Review
  - IRB Chair/Reviewer OR Convened Board Review
    - Project Approved
What does an IRB evaluate?

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk/benefit ratio</td>
<td>Risks are reasonable in relation to possible benefits</td>
</tr>
<tr>
<td>Distribution of risks/benefits</td>
<td>Certain populations are not targeted to experience risks or benefits</td>
</tr>
<tr>
<td>Consent</td>
<td>Full disclosure, comprehensible, voluntary</td>
</tr>
<tr>
<td>Protection of Vulnerable Subjects</td>
<td>Special protections are afforded to groups such as children, prisoners, etc.</td>
</tr>
<tr>
<td>Protection of Privacy &amp; Confidentiality</td>
<td>Data is gathered and used in ways that protect confidentiality and protect subjects from harm</td>
</tr>
</tbody>
</table>
1. **Expedited Review** – carried out by the IRB Chair or experienced voting member(s) of the IRB

2. **Full Board Review**

3. **Continuing Review** – interval appropriate to the degree of risk, but not less than once per year
   - No grace period
   - Criteria for IRB approval are same as initial review
IRB Annual Review and Approval – what are the Regulations?
Subpart A--

Basic HHS Policy for Protection of Human Research Subjects

Sec. 46.109  IRB review of research.
§46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:
(a) Follow written procedures in the same detail as described in §46.103(b)(4) and, to the extent required by, §46.103(b)(5).
(b) Except when an expedited review procedure is used (see §46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.
(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.
(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117.
(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.
(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(Approved by the Office of Management and Budget under Control Number 0990-0260.)
[56 FR 28012, 28022, June 10, 1991, as amended at 70 FR 36328, June 23, 2005]
What the Regulations require of You, the Researcher?
What do these Regulations require of Researchers?

• Follow the Belmont Principles
  – Respect, Beneficence, and Justice
• Submit human subject research projects to an IRB for review and on-going approval prior to expiration
• Follow other applicable regulations and institutional policies and procedures
Tell the IRB about the plan for human subject research

- Apply for IRB approval **before** conducting research involving human subjects 45 CFR 46.109, 21 CFR 56.103
After approval: Tell the IRB about any changes in human research
45 CFR 46.103 (b)(4)

• Apply for IRB approval **BEFORE implementing changes** in a protocol or consent

• **EXAMPLES:**
  • Eligibility criteria
  • Number of subjects to be recruited
  • Adding or deleting a procedure or analysis
  • Adding or changing a recruitment method (letters, flyers, fairs)
  • Change in investigators or facilities
Tell the IRB about any changes in human research 45 CFR 46.103 (b)(4)

• Apply for IRB approval before implementing changes EXCEPT when safety protections are ”necessary to eliminate apparent immediate hazards to the subject.”
  – Implement a safety change and report IMMEDIATELY to IRB.
Tell the IRB about the progress of human research

21 CFR 56.109 (f); 45 CFR 46.109 (e)

- Report progress with renewal application
  - Report data about recruited subjects
- Report updates, significant developments
  - New information that may affect subjects’ willingness to participate
- Summaries of expected and unexpected adverse events (see IRB policies)
Tell the IRB about the progress of human research

21 CFR 56.109 (f); 45 CFR 46.109 (e)

- If the project has lapsed or expired report whether or not the following activities occurred:
  1. Recruitment of subjects
  2. Enrollment of subjects
  3. Research intervention, for example, administering drugs, performing surgery, or counseling
  4. Research interaction, for example, collecting urine or blood, conducting an MRI, conducting interviews, asking for informed consent to use medical records
  5. Collection of data; and
  6. Data analysis
Tell the IRB about the progress of human research
21 CFR 56.109 (f); 45 CFR 46.109 (e)

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  4. Research interaction, for example, collecting urine or blood, conducting an MRI, conducting interviews, asking for informed consent to use medical records
  5. Collection of data; and
  6. Data analysis
Tell the IRB about the problems in human research

- Unanticipated Problems 45 CFR 46.103 (b)(5)
- Unexpected and Expected Adverse Events 45 CFR 46.103 (b)(5); 21 CFR 56, 312, 812 (also check IRB policies/guidance)
- Protocol and consent deviations 45 CFR 46.103 (b)(4); 21 CFR 56.108 (a) (3)
What Will Happen if You Don’t Follow the Regulations?
The Washington Post

Wednesday, May 12, 1999

U.S. Halts Research On Humans at Duke

University Can't Ensure Safety, Probers Find

By Rick Weiss
Washington Post Staff Writer

Among the proposals was a study that used human subjects that specifically indicated they were not aware of the risks involved.

Houston Chronicle

Some research at UTMB frozen

Federal investigation alleges inadequate patient protection

By Leigh Hopper
Houston Chronicle Medical Writer

Father's Complaint Contributes to Suspension of University's Research Trials

The Chronicle of Higher Education

Today's News

Clinical trials halted

Feds: Cancer study endangered patients

By Edward T. Pound
USA TODAY

WASHINGTON — In a continuing crackdown on mishandled medical ex-

More trials

The number of clinical trials per new drug has risen sharply.
What is Noncompliance?

Any action or activity associated with the conduct or oversight of research involving human participants that fails to comply with either the research plan as approved by a designated IRB, or federal regulations or institutional policies governing human subject research. *

*Definition – Yale University – HRPP Policy 700*
Serious Noncompliance?*

Any behavior, action or omission in the conduct or oversight of human research that, in the judgment of a convened IRB, has been determined to:

1. adversely affect the rights and welfare of participants
2. harm or pose an increased risk of substantive harm to a research participant
3. result in a detrimental change to a participant’s clinical or emotional condition or status
4. compromise the integrity or validity of the research, or
5. result from willful or knowing misconduct on the part of the investigator(s) or study staff.

Example listed in HRPP Policy 700:
• Failing to obtain and/or document a participant’s informed consent provided the IRB has not granted a waiver of consent.

*Definition – Yale University – HRPP Policy 700
Continuing Noncompliance?*

A pattern of noncompliance that, in the judgment of a convened IRB:
1. indicates a lack of understanding or disregard for the regulations or institutional requirements that protect the rights and welfare of participants;
2. compromises the scientific integrity of a study such that important conclusions can no longer be reached;
3. suggests a likelihood that noncompliance will continue without intervention; or
4. involves frequent instances of minor noncompliance, for example, repetitive protocol deviations.

*Definition – Yale University – HRPP Policy 700
IRB Noncompliance?

- Applies to anyone - investigators, study coordinators, data managers, staff, IRB members, IRB office

- 2 Types
  - Serious Noncompliance
  - Continuing Noncompliance
Examples

• Intentional violation of laws, regulations, or institutional policies governing the conduct of human research

• Subjects enrolled and harmed while on a study – e.g. failed inclusion criteria but still entered

• Research performed without IRB approval

• Research performed during lapsed approval

• Exempt research not reviewed by IRB

• Subjects enrolled without consent
Examples

• Violation(s) after notice by IRB, sponsors, institutional officials, or government regulators to report

• Refusal to comply with an IRB request, e.g. submit annual renewal before expiration

• Consistently late submissions of deviations

• Continuing to conduct exempt research after IRB orders a stop

• Repeated consent form signed, but not dated

• “PI or study team member just doesn't’t get it”
FDA Audit Most Commonly Noted Deficiencies

- Problems with patient consent
- Non-adherence to protocol
- Inadequate or inaccurate records
- Inadequate drug accountability
- Problems with IRB approval
- Failure to list all sub-investigators
- Failure to record adverse events
June 9, 2009

Michael W. Bukosky
Executive Vice President, Chief Administrative Officer
Carle Clinic Association
602 West University Avenue
Urbana, IL 61801

James C. Leonard, M.D.
Chief Executive Officer
Carle Foundation Hospital
611 West Park Street
Urbana, IL 61801

RE: Human Research Protections Under Federalwide Assurances FWA-5173 and FWA-2292

Research Project: A Clinical Trial of Adjuvant Therapy Comparing Six Cycles of 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC) to Four Cycles of Adriamycin and Cyclophosphamide (AC), with or without Celecoxib, in Patients with Node-Negative Breast Cancer
HHS Protocol Number: NSABP-B-36

Research Project: Cetuximab and/or Bevacizumab Combined With Combination Chemotherapy in Treating Patients With Metastatic Colorectal Cancer
HHS Protocol Number: CALGB 80405

Research Project: Valerian for Improving Sleep in Patients With Cancer Receiving Adjuvant Therapy
HHS Protocol Number: NCTCTG N01C5

Research Project: A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin Versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers
HHS Protocol Number: ECOG E3202
(1) We determine that the Carle IRB did not conduct continuing review of research at least once per year as required by HHS regulations at 45 CFR 46.109(e) and that Carle Clinic investigators continued to conduct non-exempt human subjects research activities beyond the expiration date of IRB approval. This determination is based on various excel spreadsheets; a March 9, 2009 report, a March 20, 2009 email correspondence, and a May 15, 2009 report. We note that all of these documents were submitted to our office after we sent Carle Foundation a February 18, 2009 email requesting that the Carle IRB forward to us a list of all currently active HHS-supported protocols approved by the Carle IRB; the list was to include protocol title; principal investigator's name; date of initial IRB approval; type of IRB review (expedited or full board); dates of all subsequent IRB continuing reviews and the type of continuing review (expedited or full board).
Carle Clinic Letter to OHRP in response to audit report:

“While we understand that according to OHRP Guidance there is no obligation to report studies for which IRB approval has lapsed due to failure to obtain timely continuing review, in light of the recent allegations made to OHRP, and in the spirit of full disclosure, we are voluntarily reporting (lapses).”
Repercussion of a Lapsed Study

OHRP Response to Carle:

Carle cited the policy incorrectly: “Please note that the OHRP guidance document entitled ‘Guidance on Continuing Review’ only addresses the issue of whether an expiration of IRB approval needs to be reported to OHRP as a suspension of IRB approval; the guidance document does not discuss whether the reporting of such incidents is required under another reporting obligation.”
Repercussion of a Lapsed Study

OHRP Response to Carle

Further, reporting may be required if…“Please note that HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) requires that an institution promptly report to the IRB, appropriate institutional officials, the department or agency head and OHRP of, among other things, any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB.”
Repercussion of a Lapsed Study

OHRP Response to Carle

Lastly, OHRP cited the following Carle deficiency:

“Continuing noncompliance, namely systemic problems involving lapses in continuing review of numerous Carle Clinic cancer studies.”
Repercussion of a Lapsed Study

OHRP required Carle to:

Required Action: Please provide us with a corrective action that will ensure that the Carle Clinic will follow its written procedures for prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP:

(a) any unanticipated problems involving risks to subjects or others;
(b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and
(c) any suspension or termination of IRB approval as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5).
Repercussion of a Lapsed Study

So.....the take home message from OHRP is:

1. Lapse = non-compliance

2. IRB must determine if non-compliance is:
   a. Serious or Continuing

If serious or continuing: The non-compliance may need to be reported to OHRP.
January 29, 2010

Yonette F. Thomas, Ph.D.
Associate Vice President for Research Compliance
Howard University
2400 Sixth Street, NW
Washington, DC 20059

RE: Human Research Protections Under Federalwide Assurance FWA-891

Research Project: Genetics of Early-Onset Depression
Principal Investigator: William Lawson, MD
HHS Protocol Number: 5R01MH075131

Dear Dr. Thomas:

Thank you for your September 28 and November 23, 2009 reports submitted in response to our July 21, 2009 request that Howard University (HU) respond to questions and concerns regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

A. Determinations regarding the above-referenced research made in our April 13, 2009 letter:

In our April 13, 2009 letter, we made the following determinations:

(1) HHS regulations at 45 CFR 46.116 state that no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative, or the institutional review board (IRB) has appropriately waived the requirements to obtain informed consent. We determined that the investigator initiated human subject research without obtaining legally effective informed consent of subjects and without the IRB appropriately waiving these requirements. In specific, we noted that the protocol envisions that identifiable private information about the subjects may be obtained from family members for research purposes prior to obtaining informed consent, but we can find no
(2) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, but not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. We determine that the IRB failed to conduct continuing review of research at least once per year and that research was conducted after expiration. In specific, the following protocols lapsed prior to IRB review and approval at the following meetings:

(a) September 23, 2009: IRB-08-MED-13; IRB-99-CC-06; IRB-08-MED-35; IRB-08-SW01.
April 21, 2011

Robert E. Burke, CPA
Managing Director
Research Foundation for Mental Hygiene
Riverview Center
150 Broadway
Menands, NY 12204

Dear Mr. Burke:

Thank you for your March 2, 2011 letter in response to our February 14, 2011 questions and concerns letter. We acknowledge the responses provided and the steps taken to modify or clarify language in a number of Research Foundation for Mental Hygiene (RFMH) & New York State Department of Mental Hygiene (DMH) institutional review board (IRB) manuals. These actions adequately address the questions and concerns noted in our February 14, 2011 letter.

In addition to resolving the questions and concerns that were previously raised, we make the following recommendations — most of which involve clarifying, correcting, including, or making explicit language regarding the regulatory provisions in one or more of the RFMH/DMH Facility IRB manuals. Please note that you are not required to adopt these recommendations.


1. Section 3.1 - Basis for Approval. We note that you have included all of the IRB approval criteria outlined in Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(a), but did not include language contained in HHS regulations at 45 CFR 46.111(b), which states that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects. We recommend that you include this statement so that the IRB approval criteria are complete.

2. Section 3.2 - Review Procedures. According to this section (as well as other RFMH/DMH Facility IRB Manuals) the IRB is required to notify only investigators (in writing) of its decision to approve or disapprove a proposed research activity, or of
3. Section F.1 – Continuing Review. According to this section, if the continuing review application is not approved by the IRB in a timely manner, the IRB approval for the study must be suspended and all subject accrual must stop, until such time as a Continuing Review report is submitted and approved by the IRB. (Continuation of research interventions in already enrolled subjects will only be permitted when the IRB finds that it is in the best interests of individual subjects to do so.) Please note that if a continuing review application is not approved by the IRB in a timely manner, all non-exempt human subjects research activities – not just subject accrual - must cease until such time as a Continuing Review report is submitted and approved by the IRB unless it is in the best interests of subjects to continue. For example, no data analysis of private identifiable information or research-related surveys/questionnaires may occur during this time. We recommend that you revise this section accordingly.

4. Section G – Submission of Protocols. We note that according to the NYSI Manual “If an application is not reviewed within 30 days of submission, the sponsor will be notified, and the application will be returned to the investigator for further information.”
Lapses/Expirations - Why Do Federal Awards Matter?
Federal Funding

- FWA reporting requirements
- Active awards (e.g. NIH, NSF, etc.)
- Assess what OHRP “engaged” research activities occurred that tie to the Statement of Work and active award
INTERVENTION with human subjects - Examples of “intervention”

- Counseling
- Physical therapy
- Surgery
- Administering drugs
- Administering devices (when done for research purposes)
INTERACTION with human subjects -
Examples of “interaction”

- Sending email or using a website to gather information
- Surveys
- Focus groups
- Collecting urine
- Collecting blood
- Conducting an MRI
- Asking for informed consent to use medical records
Determining Applicability

Other “engaged activities”
with human subjects –

- Recruitment – advertising
- Enrollment/Consenting
- Data Analysis

(when done for research purposes)
Federal Enforcement History

• Peer institutions suspended by OHRP
  – Rush Memorial Hospital (1999)
  – University of Illinois at Chicago (1999)
  – Virginia Commonwealth University (1999)
  – University of Pennsylvania (1999)
  – Duke University Medical Center (1999)
  – Johns Hopkins University (2001)
  – Washington University VA (2008)

• 2007 letters
  – Johns Hopkins University (QI/QA)
Late at night, and without permission, Reuben would often enter the nursery and conduct experiments in static electricity.
Questions?
Administrator Guidance
Avoiding and Dealing with a Protocol Lapse

Objectives
- Tools
- What to do after notification of a lapse
Administrator Guidance

• Tools to help assist investigator with avoiding a lapse.
  – Report
    • COEUS Access
    • Call IRB
  – E-mail
    • Change in the works to copy administrators
Award Management

• When there is a lapse in a protocol:
  – Individuals from the IRB, GCA and GCFA will review the information (including meeting with the investigator and study personnel) in order to determine what activity occurred during the lapsed period:
    • Did human subject research continue during the lapsed period?
      – Specifically what type of human subject research activity (e.g. recruitment) occurred during the lapsed period?
    • Was effort devoted and charged or other charges related to human subjects research made to the award?
GCFA will follow-up with the department administrator to review all expenses that occurred during the lapsed period.

- Charges for human subject research for the lapsed protocol must be removed from the award.
- If the project scope includes non-human subject aspects, those activities may continue and related charges are allowed on the award.

GCA will review the situation to determine if the Grants Management Officer (if NIH) and/or Program Officer are to be notified.

- Based on the significance of the situation and the impact on the project.
- Has the lapse caused a delay or impaired the ability of Yale to meet the objectives of the project.
Summary Questions

If no other research but human subjects research is conducted on the award, what can continue to be charged to the award, if anything?

A) Salaries
B) Supplies
C) Both A & B
D) None of the above

Answer: D) None of the above since the project contains no other research aims which does not include human subjects research.
Summary Questions

You are responsible for discussing with the PI what work was conducted during the lapsed period?

True or False

Answer: False, the IRB will lead discussions with the PI. You will be asked to participate and work with GCFA in identifying and removing charges as appropriate.
Questions?