IRB Operations

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Course Objectives

• Understand the regulatory requirements for IRB operations

• Understand the implementation of these regulatory requirements in the SOPs
IRB Membership Requirements
§46.107 IRB membership
§56.107 IRB membership

- (a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

- (b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution’s consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

- (c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

- (d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
§46.304 Composition of Institutional Review Boards where prisoners are involved.

- In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:
  - A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
  - At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.
IRB Membership Requirements
Implementation

- HRP-010 - SOP - Annual Evaluations of the Human Research Protection Program
- HRP-080 - SOP - IRB Formation
- HRP-083 - SOP - IRB Membership Removal
- HRP-308 - WORKSHEET - IRB Composition
§46.103 Assuring compliance with this policy
§56.115 IRB records.

- A list of IRB members identified by ... any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant.
Consolidated regulatory and guidance requirements for IRB rosters

- Name
- Earned degrees
- Gender
- Representative capacity
  - Scientific/nonscientific status
  - Affiliation status (whether the member or an immediate family member of the member was affiliated with the organization)
  - Vulnerable populations about whom the member is knowledgeable about or experienced in working with.
- Indications of experience such as board certifications, licenses, etc., sufficient to describe each member’s chief anticipated contributions to IRB deliberations
- Any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant
- Status as an alternate or primary member
- The primary members or class of primary members for whom each alternate member can substitute.
IRB Roster Implementation

- HRP-080 - SOP - IRB Formation
- HRP-082 - SOP - IRB Membership Addition
- HRP-083 - SOP - IRB Membership Removal
- HRP-602 - DATABASE - IRB Roster
IRB Member Conflicting Interests
§46.107 IRB membership
§56.107 IRB membership

• No IRB may have a member participate in the IRB’s initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.
IRB Member Conflicting Interests Implementation

- HRP-001 - SOP - Definitions
- HRP-041 - SOP - IRB Meeting Conduct
- HRP-042 - SOP - IRB Meeting Attendance Monitoring
- HRP-043 - SOP - IRB Meeting Minutes
- HRP-050 - SOP - Conflicting Interests of IRB Members
- HRP-402 - CHECKLIST - Non-Committee Review
Definition of Conflicting Interest

• Related to the Research: A financial interests is Related to the Research when the interest is in:
  – A sponsor of the research;
  – A competitor of the sponsor of the research;
  – A product or service being tested; or
  – A competitor of the product or service being tested.

• Immediate Family: Spouse, domestic partner, dependent children, parents, siblings, and in-laws.

• Conflicting Interest: An individual involved in research review is automatically considered to have a conflicting interest when the individual or the individual’s Immediate Family have any of the following:
  – Involvement in the design, conduct, or reporting of the research.
  – Ownership interest, stock options, or other ownership interest Related to the Research of any value exclusive of interests in publicly-traded, diversified mutual funds.
  – Compensation Related to the Research of any amount in the past year or of any amount expected in the next year, including compensation for costs directly related to conducting research.
  – Proprietary interest Related to the Research including, but not limited to, a patent, trademark, copyright or licensing agreement.
  – Any other reason for which the individual believes that he or she cannot be independent.
Consultants to the IRB
§46.107 IRB membership
§56.107 IRB membership

• An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.
Consultants to the IRB Implementation

- HRP-040 - SOP - IRB Meeting Preparation
- HRP-041 - SOP - IRB Meeting Conduct
- HRP-051 - SOP - Consultation to the IRB
- HRP-311 - WORKSHEET - Criteria for Approval and Additional Considerations
IRB Procedures
§46.103 Assuring compliance with this policy
§56.108 IRB functions and operations

• Written procedures which the IRB will follow
  – For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;
  – For determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and
  – For ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

• Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of
  – Any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and
  – Any suspension or termination of IRB approval.
Required Written Procedures
For IRB review

• For conducting initial and continuing review of research
• For reporting findings and actions to the investigator
• For reporting findings and actions to the institution
• For determining which projects require review more often than annually
• For determining which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review
• For ensuring prompt reporting to the IRB of changes in research activity
• For ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects
Required Written Procedures
For reporting of information

• Any unanticipated problems involving risks to human subjects or others
• Any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB
• Any suspension or termination of IRB approval
Required Written Procedure: For conducting initial and continuing review of research

- Convened IRB
  - HRP-043 - SOP - IRB Meeting Minutes
  - HRP-040 - SOP - IRB Meeting Preparation
  - HRP-041 - SOP - IRB Meeting Conduct
  - HRP-042 - SOP - IRB Meeting Attendance Monitoring

- Expedited Review Procedure
  - HRP-032 - SOP - Non-Committee Review Conduct
  - HRP-030 - SOP - Designated Reviewers
  - HRP-031 - SOP - Non-Committee Review Preparation

- All Reviews
  - HRP-050 - SOP - Conflicting Interests of IRB Members
  - HRP-051 - SOP - Consultation to the IRB
  - HRP-052 - SOP - Post-Review
Required Written Procedure: For reporting findings and actions to the investigator

- HRP-052 - SOP - Post-Review
- HRP-303 - WORKSHEET - Communication of Review Results
Required Written Procedure: For reporting findings and actions to the institution

• HRP-043 - SOP - IRB Meeting Minutes
Required Written Procedure: For determining which projects require review more often than annually

- HRP-311 - WORKSHEET - Criteria for Approval and Additional Considerations
Required Written Procedure: For determining which projects need verification ...

- For determining which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review

- HRP-311 - WORKSHEET - Criteria for Approval and Additional Considerations
Required Written Procedure: For ensuring prompt reporting to the IRB of changes in research activity

- HRP-103 - INVESTIGATOR MANUAL
Required Written Procedure: For ensuring that changes in approved research, ...

- For ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects

- HRP-103 - INVESTIGATOR MANUAL
Required Written Procedure:

• To ensure prompt reporting to the IRB, appropriate institutional officials, and regulatory agencies of:
  – Any unanticipated problems involving risks to human subjects or others
  – Any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB
  – Any suspension or termination of IRB approval
What must the IRB review?
What must the IRB review to protect subjects?
What must the IRB committee review?

- Research requesting approval
  - Proposed research
  - Continuing reviews
  - Proposed modifications (with one exception)

- Other information
  - Unanticipated problems involving risk to subjects or others
  - Serious or continuing non-compliance with the regulations and the requirements of the IRB
  - Suspensions and terminations of IRB approval
To whom do the regulations refer when they say “prompt reporting to the IRB”?
When the regulations require prompt reporting to the IRB, what is expected of the IRB?
When do these have to be promptly reported to the IRB?

- Adverse event
- Protocol deviation
- DSMB report
- Revised investigator brochure
- Information notice from the sponsor
- Interim results
IRB Workflow

New information
*From anywhere*

Does the information represent any of the following:
- Unanticipated problem involving risk to subjects or others
- Serious or continuing non-compliance with regulations or the requirements of the IRB
- Suspension or termination of IRB approval

**YES**
**NO**

**Convened IRB**

- Report to regulatory agencies and appropriate institutional officials

**No IRB action**

Tell investigators what to report in language they can understand

Have IRB staff determine whether reported information falls into one of these categories
Implementation

- HRP-020 - SOP - Incoming Items Directed to the IRB
- HRP-024 - SOP - New Information
- HRP-041 - SOP - IRB Meeting Conduct
- HRP-306 - WORKSHEET - Review of Information Items
- HRP-303 - WORKSHEET - Communication of Review Results
- HRP-516 - TEMPLATE LETTER - External Report
- HRP-520 - TEMPLATE LETTER - Review of Information Item
What are “unanticipated problems involving risks to subjects or others?”
The following information is provided to the IRB office:

A subject in a bone marrow transplant trial for advanced leukemia died of sepsis.
The following information is provided to the IRB office:

A subject in a research study evaluating marital counseling dies of a heart attack. The subject was 53 years old and had diabetes and hypertension.
The following information is provided to the IRB office:

A subject in a research study gets an investigational drug and immediately begins to vomit. The vomiting subsides in a couple of hours. The subject goes home, returns the next day for a second dose and the same thing happens.
The following information is provided to the IRB office:

A subject in a research study gets an investigational drug and immediately begins to vomit. The vomiting subsides in a couple of hours. The subject goes home, returns the next day for a second dose and the same thing happens.

- This occurs in a multisite study at a site NOT under the jurisdiction of your IRB.
The following information is provided to the IRB office:

A blood sample for a drug level was obtained from a subject and sent to the lab as part of a research study on this drug. The blood sample broke in transit. By the time a second blood level was obtained and analyzed the subject was found to have a critically low blood level.
The following information is provided to the IRB office:

A blood sample for a drug level was not obtained from a subject because a member of the research team forgot to get a sample. A second blood level was obtained and the subject was found to have a critically low blood level.
The following information is provided to the IRB office:

An updated investigator brochure.
The following information is provided to the IRB office:

The sponsor sends a letter to the investigator noting that it is putting the trial on a “clinical hold” pending completion of review of the data by the DSMB.
The following information is provided to the IRB office:

The sponsor sends a letter to the investigator noting that the DSMB has completed its review and found that no changes to the protocol are needed.
The following information is provided to the IRB office:

The sponsor sends a letter to the investigator noting that the DSMB has completed its review and found that the experimental group is experiencing significantly more insomnia than the control group.
The following information is provided to the IRB office:

A member of the research team took blood from an HIV positive subject and splashed it in his eye. Now he will have to undergo anti-retroviral prophylaxis.
The following information is provided to the IRB office:

A research team member reports that a laptop containing subject information was stolen.
The following information is provided to the IRB office:

A research team member reports that a laptop containing subject information was stolen.

- This occurs in a multisite study at a site NOT under the jurisdiction of your IRB.
The following information is provided to the IRB office:

**Intensive versus Conventional Glucose Control in Critically Ill Patients**

*The NICE-SUGAR Study Investigators*

**Conclusions** In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.

- Your IRB is overseeing an investigator-initiated study of intensive versus conventional glucose control.
The following information is provided to the IRB office:

Information for Healthcare Professionals: Varenicline (marketed as Chantix) and Bupropion (marketed as Zyban, Wellbutrin, and generics)

USFDA ALERT [7/1/2009]:
USFDA has required the manufacturers of the smoking cessation aids varenicline (Chantix) and bupropion (Zyban and generics) to add new Boxed Warnings and develop patient Medication Guides highlighting the risk of serious neuropsychiatric symptoms in patients using these products. These symptoms include changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide.

• Your IRB is overseeing an ongoing study of bupropion.
The following information is provided to the IRB office:

DOCTOR ACCUSED OF SEXUAL ABUSE

BRENDAN LYONS Staff writer

Section: CAPITAL REGION,  Page: B1
Date: Friday, November 8, 2002

A well-known pediatric neurologist from Slingerlands has been charged with having sexual contact with two young boys during medical exams at his office, police said. In both cases, Dr. Phillip S. Riback, 45, of Mayfair Drive, asked the boys’ mothers to leave the exam room just before the separate incidents took place in December and January, police said.

• Your IRB is overseeing three ongoing studies where this individual is the principle investigator.
What are “unanticipated problems involving risks to subjects or others?”
Definition of unanticipated problem involving risks to subjects or others

- Unanticipated (new information previously unknown to the IRB)
  
  AND
  
- Involves risks to subjects or others (indicates that risks to subjects or others has increased)
## Decision matrix

<table>
<thead>
<tr>
<th>Problem indicates that subjects or others are at increased risk of harm</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>The IRB already knew this problem could occur and previously included this consideration in its review. AND Problem does not involve risk to subjects. <strong>This is NOT an unanticipated problem involving risks to subjects or others and no action is necessary to protect subjects.</strong></td>
<td>Problem involves risk to subjects BUT The IRB already knew this problem could occur and previously included this consideration in its review. <strong>This is NOT an unanticipated problem involving risks to subjects or others and no action is necessary to protect subjects.</strong></td>
</tr>
<tr>
<td>Yes</td>
<td>The IRB did not know this problem could occur <strong>BUT</strong> Problem does not involve risk to subjects. <strong>This is NOT an unanticipated problem involving risks to subjects or others and no action is necessary to protect subjects.</strong></td>
<td>The IRB did not know this problem could occur <strong>AND</strong> Problem involves risk to subjects or others. <strong>This IS an unanticipated problem involving risks to subjects or others. Convened IRB review is necessary to protect subjects. Reporting to regulatory agencies and appropriate institutional officials is required.</strong></td>
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What about the OHRP definition?

OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome (including adverse events) that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.”
Problems with OHRP guidance

- States that anything that meets the three criteria is an unanticipated problem involving risks to subjects or others, but does not state that anything that does not meet the three criteria is *not*.

- OHRP defines “related” to mean “there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)” but later says “related” means “some relationship to the research.”
Definition of unanticipated problem involving risks to subjects or others

• Unanticipated (new information previously unknown to the IRB)

AND

• Involves risks to subjects or others (indicates new or changed risks to subjects or others)

Shorthand: Information that indicates a new or changed risk

NOTE: This definition is consistent with OHRP guidance.
Handling the information when it gets to the IRB office is the easy part.
Hard part: What do you tell investigators to report to the IRB?
What do investigators need to report to the IRB?

• What should investigators report to ensure that your “Inbox” will contain all?
  – Unanticipated problem involving risk to subjects or others
  – Serious or continuing non-compliance with regulations or the requirements of the IRB
  – Suspension or termination of IRB approval
What do investigators need to report to the IRB?

• Don’t simply tell investigators to report “unanticipated problems involving risks to subjects or others.”

• Tell investigators the problems they need to send to the IRB so that among those problems will be the unanticipated problems involving risks to subjects or others.

• HRP-224 - FORM - Reportable New Information
Which adverse events cannot be unanticipated problems involving risk to subjects or others
Adverse events

• Adverse events represent harms not risks.
• Adverse events represent a single data point.
• 99% of adverse events are not unanticipated problems involving risks to subjects or others.
• 99% of unanticipated problems involving risks to subjects or others are not adverse events.
• If the majority of your unanticipated problems involving risks to subjects or others are adverse event, you are not protecting subjects.
• The proper management of adverse events is in the protocol as part of adequate provisions to monitor the data to ensure the safety of subjects.”
Reporting requirements for adverse events

• Unexpected
  – The specificity or severity of the harm is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, with the risk information described in the general investigational plan or elsewhere in the current application, as amended.)

• Possibly or probably related
  – More likely than not the adverse event was caused by the research procedures.
OHRP Guidance

- Investigators should report adverse events to the IRB when they
  1. Are unexpected,
  2. Are at least possibly related to (“caused by”) the research procedures, and
  3. Suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. There are several problems with this guidance.
Problems with OHRP guidance

• What if the investigator decides the adverse event is unexpected, caused by the research procedures, but does not suggest that subjects are at increased risk?
• Who spends their day studying data for causal relationships?
• Who spends their day studying information for risk assessment?
What protocol deviations cannot be unanticipated problems involving risk to subjects or others?
What protocol deviations cannot be serious or continuing non-compliance?
What investigator brochures modifications cannot be unanticipated problems involving risk to subjects or others?
What DMSB reports cannot be unanticipated problems involving risk to subjects or others?
What sponsor reports cannot be unanticipated problems involving risk to subjects or others?
The most common unanticipated problems involving risks to subjects or others

- New information from the regulatory agencies that indicates new or changed risks
- New information from the sponsor (investigator brochure, DSMB report, interim data, sponsor report.)
- New literature that indicates new or changed risks
§46.115 IRB records
§56.115 IRB records

• An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:
  – Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.
  – Minutes of IRB meetings …
  – Records of continuing review activities.
  – Copies of all correspondence between the IRB and the investigators.
  – A list of IRB members identified by name; earned degrees; …
  – Written procedures for the IRB …
  – Statements of significant new findings provided to subjects
Requirements to “find and document”

- Expedited review
- Waiver or alteration of consent
- Waiver of written documentation of consent
- Pregnant women, neonates
- Prisoners
- Children
- Planned emergency research

- All implemented on corresponding checklists
IRB Meeting Minutes
§46.115 IRB records
§56.115 IRB records

- Minutes of IRB meetings which shall be in sufficient detail to show:
  - Attendance at the meetings
  - Actions taken by the IRB
  - The vote on these actions including the number of members voting for, against, and abstaining
  - The basis for requiring changes in or disapproving research
  - A written summary of the discussion of controverted issues and their resolution.
Consolidated regulatory and guidance requirements for minutes

- Attendance of IRB members at the meetings for each action of the IRB including IRB members who vote as an alternates in place of another IRB member.
- Actions taken by the IRB including separate deliberations for each action
- The vote on these actions including the number of members voting for, against, and abstaining
- The basis for requiring changes in research
- The basis for disapproving research
- A written summary of the discussion of controverted issues and their resolution
- When an alternate IRB member replaced a primary IRB member
- Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document
- The names of IRB members who left the meeting because of a conflicting interest along with the fact that a conflicting interest was the reason for the absence.
- Unless documented in the IRB records determinations required by the regulations and protocol-specific findings supporting those determinations for:
  - Waiver or alteration of the consent process
  - Research involving pregnant women, fetuses, and neonates
  - Research involving prisoners
  - Research involving children
- Unless documented in the IRB records, the frequency for the next continuing review for each protocol’s initial and continuing review
- The rationale for significant risk/non-significant risk device determinations
IRB Meeting Minutes Implementation

- HRP-043 - SOP - IRB Meeting Minutes
- HRP-501 - TEMPLATE MINUTES
IRB Operations

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