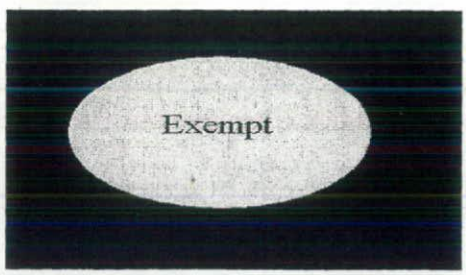
"Exempt" Research

- Six categories, defined by 45 CFR 46 (32 CRF 219.010)
- Determination made locally to accept all, some, or none of the categories
- Determination by IRB or other designated reviewer
- Research must fall into one or more of the categories to be exempt
- Procedure to determine exemption must be clear, PI cannot make determination
- May still require consent or other safeguards (Belmont principles)

Some Examples of Exempt

- Studies of normal educational practices in commonly accepted educational settings
- Research involving educational tests or passive observation of public behavior that is anonymous or benign
- Research involving surveys or interviews of adults that are devoid of risk OR anonymously recorded

Is It "Exempt"?



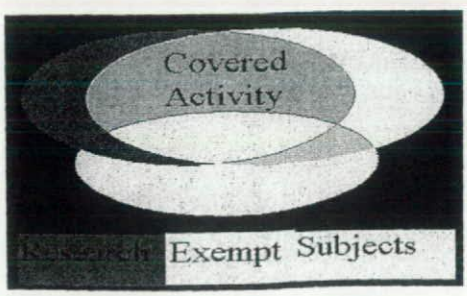
Reviewers may still determine

- The survey has risk, so it cannot be exempt
- State and local laws my prohibit an exemption
- Exempt study may still need consent
- Exempt study may have ethical concerns

Exemption Categories:

- (1) Educational research
- (2-3) Tests, surveys, interviews or public observation
- (4) Research on existing public or de-identified data or specimens
- (5) Federal demonstration projects
- (6) Taste and food evaluation

Is It A "Covered Activity"?



Work it through

- An investigator asks for coded information on the treatment outcomes of patients treated for arthritis with Drug A versus Drug B from the patients. These are not the investigator's patients. The only involvement of the treating physician is to provide coded information to the investigator.
  - Is this research? **YES** "systematic investigation for generalizable knowledge"
  - Does this involve human subjects? " **NO**, if the investigator and the treating physician enter into an agreement prohibiting the release of the key to decipher the code to the investigator under any circumstances, until the individuals are deceased..

"Ok if it is not exempt, The IRB can expedite it. This is quick, right? "

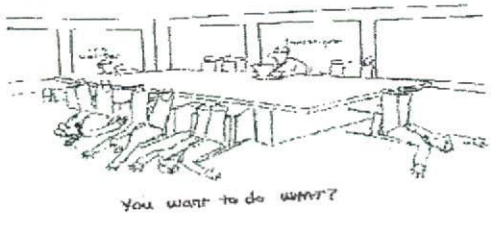
Work it through

- The same investigator obtains individually identifiable information on the treatment outcomes of patients treated for arthritis with either Drug A or Drug B by viewing patients existing individually identifiable medical records at the clinics where the patients were treated. The investigator records the patients treatment outcomes in a coded manner that could permit the identification of the patients.
  - Is this research ? YES
  - Does it involve Human Subjects? YES, the investigator is obtaining identifiable private information from patients medical records.
  - Is this exempt? NO, the investigator is recording the information in a coded manner, thus allowing the subjects to be identified indirectly through identifiers linked to the subjects.

What is an IRB? Does it mean Inconsistent /Irrational Review Board?

What is this?

- Collection and use of information from public database (i.e crime rates in different cities) for a publication.
- Sending questionnaires to elementary schoolteachers to ask their opinion of whether a new curriculum worked well in the classroom. The information will be published in an educational magazine
- Conducting an anonymous interview of teachers about how much time teachers spend on grading papers and preparing a lecture. The information will be published in an educational magazine
- Obtaining specimens from pathology without names, med rec # or dates but diagnosis
  - Is it research?
  - Does it involve human subjects
  - Is it exempt



A Typical IRB Meeting

What is an IRB ?

- At Least 5 Members, both genders
- Varied professions, scientific, nonscientific
- Member not otherwise affiliated with the institution hosting IRB
- Experience , Expertise, Diversity
- Sensitivity to community attitudes
- Knowledge of institutional commitments and regulations, applicable law, standards of professional conduct
- Knowledgeable & experienced with vulnerable subjects
- Special competencies of Ad Hoc consultants

Some Cautionary Words for IRB's:

- Tendency to confuse " non-scientific" member with community/unaffiliated representative
  - Regs require non-scientist to be present as part of a quorum.
- IRBs underutilize consultants
- IRBs lack diversity
- IRB membership is time consuming/need incentives

IRB Autonomy and Support

- Research approved by the IRB may be subject to further appropriate review and approval of disapproval by institution, However, those officials may not approve research if it has not been approved by IRB

–45 CFR 46.112 and 21 CFR 56.11

Expedited Review

- Expedited does not mean quicker
- Rigor of review the same, number of reviewers different
- Review carried out by IRB chair or by one or more experienced reviewers
- Reviewers may approve or modify, but may not disapprove

What Does an IRB Do?

- Approve, Disapprove, or Modify
- Conduct Continuing Review
- Observe / Monitor /Audit (or 3rd party)
- Suspend or Terminate Approval

An IRB may use the expedited review procedure to review either or both of the following:

(1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

"It is not invasive so it must be minimal risk"

This is not correct. Think of risk of criminal/civil liability, financial risk, employment risk, stigmatization, insurability, embarrassment in addition to physical risk when deciding if risk is truly minimal.

Assessment of minimal risk:

The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests

Eligible for Expedited Review: (Initial Review)

- Clinical studies: IND/IDE NOT required
- Blood sample collection (routine methods –small amounts)
- Prospective collection of biological samples-noninvasive means
- Data collected though noninvasive means (routinely practiced in clinical settings)
- Materials (data, documents, specimens etc.) have been collected or will be collected for non-research purposes
- Collection of voice, video or digital data for research purposes
- Individual or group behavior, surveys, interviews, oral histories

Eligible for Expedited Review: (Continuing Review)

- Continuing review of research with no further direct subject participation
- Continuing review of minimal risk research (not under IND or IDE) where no additional risks have been identified

Caution for IRBs: Expedited Procedures

- IRBs need to develop mechanism to keep all members advised of research which has been approved by expedited review
- Procedure needs to be on list
- Expedited does not mean cursory, documentation of substantive review is essential
- Err on the side of full review, if any question
- Expedited review is an option
- Many methods to conduct expedited review

"Well if it cannot be exempt or expedited, that must mean full review"

(Full "Convened" Committee)

Criteria For Approval

45 CFR 46.111

- Risks are minimized (not eliminated)
- Risks are Reasonable in relation to anticipated benefit
- Equitable subject selection
- Informed consent process
- Informed consent documentation
- Data monitored for safety
- Confidentiality/privacy maintained
- Vulnerable populations protected

Full Review Means

- A full quorum is assembled (at least half of the members, includes nonscientist)
- All members participate in discussion and make comments (plenary review);
- Decision is rendered by a majority of the assembled quorum.
- No member with a conflict of interest participates in the decision
- Numerical vote is taken and recorded

Criteria: Risks are minimized

- Procedures are consistent with sound research design and do not unnecessarily expose subjects to risk
  - Even if question is important, if methods aren't likely to answer it, study is unethical
    - not feasible
    - poor measures
    - inadequate sample size
    - poor statistical analysis
    - biased reporting (or non-reporting

What should the IRB consider when it reviews research?

An IRB will consider:

- Can alternative procedures answer the scientific question and reduce likelihood of harm?
- Can fewer procedures answer the scientific question?
- Must consider physical, psychological , social, legal and economic risks
- Are procedures that answer the question being done anyway?

Risks are reasonable in relation to anticipated benefits

- What are the risks and benefits?
- Are the risks and benefits clearly defined and honest?
- Need to consider magnitude and probability

Provision to monitor the data collected & ensure the safety of subjects

- Every protocol needs a plan
- Who reviews data? (PI, monitor, DSMB, internal committee)
- What data are reviewed
  - Untoward events
  - Serious adverse events
  - Efficacy data
- When are data reviewed
- Safety provisions
  - SAE, unanticipated problems
  - Stopping rules

Equitable selection

- Selection must be
  - Fair, Just, Equal
  - Burdens/Benefits distributed fairly
  - No population is unfairly targeted/excluded
- What factors affect selection?
  - Inclusion Criteria
  - Exclusion Criteria
  - Recruitment practices
  - Setting of research
  - Purpose of research

Provisions for Privacy and Confidentiality

- Privacy refers to persons and their interest in controlling access to themselves
  - Will subjects think information is investigator's business? Where do you conduct research, how contact subjects
- Confidentiality refers to agreements with the subject about how the data will be handled
  - Can confidentiality be pledged?
  - Are there legal/ethical requirements?
  - Methods to assure confidentiality

Informed Consent

Process: Informed consent will be sought from each prospective subject or legally authorized representative

Informed consent will be documented

Consideration of Vulnerability

- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards necessary
  - Research must be important to vulnerable population
  - Research can't be answered without inclusion of vulnerable population
  - Risk/benefit relationship is appropriate
  - Consider
    - Assessment of capacity
    - Permission of representative
    - Assent
    - Witness to consent

When does the full IRB need to review a PI response?

- When the IRB requests substantive modifications or is information seeking, IRB approval must be deferred, pending subsequent review by the full IRB
- The IRB must stipulate specific revisions to allow a designated reviewer to later approve the research on behalf of the IRB, (simple concurrence)

What should the IRB consider during continuing review?

- Are both risks and anticipated benefits accurately identified, are they as anticipated?
- Has new information become available and relevant to risk/benefit determination?
- Have there been adverse events, have they been reported?
- Has study recruitment occurred as anticipated, if not why?
- What is the justification for continuing the research?

"It seems like we just granted final approval, what is all this additional paperwork"

Continuing Review

The PI changed her mind, what should happen? Amendments and Revisions

Continuing Review

IRBs are required to conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year . They also have the authority to observe or have a third party observe the consent process and the research

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

Changes in protocols

- All revisions/amendments require review
- Require approval before implemented unless to assure immediate safety of subject(s)
- Understand reason for change
- Understand whether the change impacts risk/benefit assessment
- Check to see if the consent requires revision
- IRB determines what type of review is required.

"Tell me about Informed Consent"

Process

Documentation

Alterations and Waivers

A coercive informed consent session.

The Informed Consent Process

General Requirements:

- Unless waived by the IRB, the investigator must obtain the legally effective informed consent of the subject or the subject's legally authorized representative.
- "Legally" defined by state/international law. (also age of majority)
- Must provide the subject sufficient opportunity to consider participation and minimize undue influence

Informed Consent is a Process

It begins when you first approach a potential subject and it continues after a form is signed:

- Consent is a PROCESS in which...
  - You disclose relevant information
  - The potential subject has opportunity to ask questions
  - You answers questions
- The consent form is a permanent record of...
  - The information you conveyed
  - The fact that the process occurred
  - The subject's willingness to participate

General Requirements

- Information must be in language understandable to the subject.
- May not include exculpatory language
- The IRB has the authority to observe or have a third party observe the consent process and the research

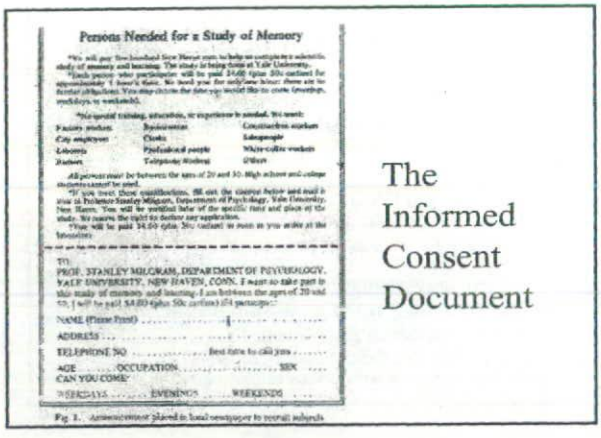
What needs to be considered for the informed consent process

- Recruitment is part of process
  - Plans and materials must be reviewed (posters, public service, scripts)
- Time, place and person obtaining consent important
- How do you know subject comprehends the information?
- Is translator or interpreter required? Does consent need to be in another language?
- Share new information with subjects - willingness to continue to participate
- Revisit consent- long term studies, capacity may change

Elements of Informed Consent

OPRR 1991
45 CFR 46.116

- Description of procedures
  - what happens to subject,
  - what does the subject need to do as part of the research
  - expected duration, how long, how often
- Description of potential risks
  - what are the risk (physical , psychological , social)
  - how likely is it they will occur
  - what will be done if they do occur
- Description of potential benefit
  - what are the potential direct benefits
  - how likely is it they will occur
  - what are the indirect benefits



Persons Needed for a Study of Memory

TO:
PROF. STANLEY MILGRAM, DEPARTMENT OF PSYCHOLOGY,
YALE UNIVERSITY, NEW HAVEN, CONN. I want to take part in
NAME (Please Print) .....
ADDRESS .....
TELEPHONE NO. .....
AGE ..... OCCUPATION ..... SEX ....
CAN YOU COME:
WEEKDAYS ..... EVENINGS ..... WEEKENDS ....

Fig. 1. Announcement placed in local newspaper to recruit subjects

The Informed Consent Document

Elements of Informed Consent

45 CFR 46.116

- Alternatives
  - what happens if you do not participate
  - can you get or do the same thing without participating
  - what else is available to you if you do not participate
- Confidentiality
  - how will information, or fact subject is participating be kept confidential
  - who will know or need to know
  - where and how will data be stored
  - who will inspect or review records

Elements of Informed Consent

OPRR 1991
45 CFR 46.116

- Research acknowledgement
  - explain this is research
  - explain what part is research
  - use the word research
- Purpose of the study
  - why is the research being done
  - why are you asking subject to participate

Elements of Informed Consent

45 CFR 46.116

- Compensation for Injury/Medical treatment (greater than minimal risk protocols)
  - if you are injured who will pay
- Who will answer questions
  - about study
  - about being a research subject
  - about injuries
- Participation is voluntary

Other Elements As Necessary

- The fact there may be unforeseeable risks
- Involuntary termination of participation
  - Under what circumstances (noncompliance, lack of funding
- Additional research costs
- Consequences of subject withdrawal

Short Form is an Alternative

- IRB approves a written summary of what is to be said and a short consent
- Written short consent document states that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative.
- Requires a witness to the oral presentation.
- Required Signatures
  - Only the short form itself is to be signed by subject
  - Witness signs both the short form and a copy of the summary,
  - Person actually obtaining consent signs a copy of the summary.
  - A copy of the summary is given to the subject or the representative, in addition to a copy of the short form.

Other Elements As Necessary

- Significant new findings will be reported to subject
- Approximate number of subjects
- Payments/Reimbursement
  - How much
  - To whom
  - Schedule for payment

You cannot get written consent in a telephone survey!

What should happen?

Informed Consent Documentation

- Written form approved by IRB
- Signed and dated by subject or legally authorized representative
- Copy given to subject or representative, maintain a copy

Exceptions to Documentation

- Consent is only record linking subject and research; link poses risk
- Subject should be asked if he/she wants documentation
- Or, no more than minimal risk and involves procedures for which consent not normally required outside context of research

When You Use Exception to Documentation

- All elements need to be covered, just in another form
  - Information sheet
  - Cover letter
  - Verbal information (scripts)
- IRB will need to review and approve consent materials
- Consent is obtained just not as a written document

FDA Exceptions to Informed Consent

- Life-threatening condition necessitating use of test article
- Inability to communicate with subject
- No time to obtain consent from legally authorized representative
- No alternative approved method

Can the IRB ever approve a complete waiver of informed consent or sections of consent? In other words no consent or not all elements are included.

Other Languages/Cultures

- Is there a need to translate the consent?
- Recognize many dialects of same language exist
- Avoid using interpreters with English consent when possible
- Is back translation necessary?
- In addition to translated consent , need study personnel who can speak the language
- Take into consideration cultural issues
  - Some cultures avoid written contracts
  - Does a husband need to sign for a women
  - Is community consent or a trial chief consent recognized instead of individual consent
- Has a local site reviewed the protocol and approved the consent form and process

YES: Requirements for Waiving Informed Consent (not FDA)

- Research is no more than minimal risk
- The rights and welfare of subject are not adversely affected
- Research could not be practicably conducted without the waiver
- Subjects provided with pertinent information after participation

FDA does not recognize waivers except:

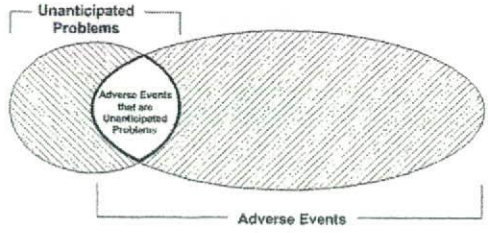
Statements from Actual Consent Forms

- " We will insert 3 catheters, one in each arm."
- "The investigator at his/her absolute discretion may terminate the procedures and/or the research subjects at any time"

Translation errors

- English to Vietnamese "Randomization' translated to "Chaos"
- English to Chinese "Double Blind" to "Blind in Both Eyes"

IRBs need to widen focus to include broader categories of what needs to be reported as an unanticipated event that involves risks to subjects or others



OHRP Draft Guidance document, October 11, 2005

If there is an adverse event or unanticipated problem involving risk what should happen? Are there other reporting/documentation requirements?

Unanticipated Event Involving Risk

- Unanticipated events/problems involving risks must be reported to IRB in a timely manner according to institutional guidelines
  - One type is serious and unexpected events thought likely to be related
  - Loss of research data with identifiers
  - Subject getting upset with interviewer or types of questions
  - Subject complaints should be reported
- Provide interpretation of event and description of precautions taken to prevent reoccurrence

Unanticipated Problem

A unanticipated problem is any <u>event or outcome</u> that meets the following three unanticipated problem criteria:

1) It is related or possibly related to the research

2) The subject or other individual is placed at greater risk of harm than initially anticipated by the IRB

3) It is unexpected

NOTE: An event or outcome refers to 1) an event involving risk to the subject or others (e.g., an AE, non-compliance, a protocol deviation) or 2) new information on risk which becomes available to the PI or IRB.

Other Reporting Requirements

- Report to IRB, Institution, OHRP, Agency
  - unanticipated problems involving risk
  - serious or continuing noncompliance
  - suspension or termination
- The IRB reports to OHRP membership changes, modifications to human subject protection program

"Can the IRB suspend and/or terminate research?"

- When research is non-compliant or associated with unexpected serious harm
- Must provide investigator with reasons for the action
- Must report promptly to the PI, institutional officials, FDA and the Department or Agency head

Document, Document, Document

- Research protocols
- Special findings, (children, prisoners, waivers of consent)
- Correspondence
- IRB application/approvals
- Continuing reviews
- Signed consent/assent forms
- Original data
- Regs require three years after completion

付録 2. PRIM&R セミナー資料

倫理審査委員会事務局教育用スライド

(IRB administrator 101)

(研究分担者:山上須賀、他)

IRB Administrator 101: Introduction

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September 2008

Workshop Format*
3 Components

- Identify Components of Human Research Protection Program Framework
- Examine 10 of 12 Administrator Responsibilities
- Share a Philosophy of Research Administration

*IRB Workshop Handouts

Disclaimer

Views Expressed in This Workshop are Those of the Speaker and Not Necessarily of the University of Kentucky

Overview: Components of a Human Research Protection Program

Administrator 101 Workshop Purpose

To Provide a Basic Overview of Information a New IRB Administrator Needs to Know to Fulfill Responsibilities

HRPP

Human Research Protection is a Shared Responsibility

Human Research Protection Program: Key Players

- Institutional Officials
- IRB – Members/Chair
- IRB Administrators
- Investigators
- Research Staff
- Internal Others (e.g., Investigational Drug Service, Radiation Safety)
- External (Sponsor, Subject, Regulatory Agency)

HRPP: Essential Components

- Education
- Policy
- Procedures
- Protocol Review
- Conduct of Study
- Study Monitoring
- Program Assessment

Which HRPP Player is Responsible for Which Function?

Who is Responsible?

- Different in Each Program
- You Need to Find Out Who Does What in Your Program
- May Find No One Responsible for Selected Functions

Examples
Typical Responsibilities of:

- Institution
- IRB
- PI
- IRB Administrator

Institution Responsible For:

1. Setting Tone for Culture
2. Complying with Regulations
3. Establishing Appropriate Number of IRBs
4. Providing Sufficient Resources

Institutional Responsibilities May be Delegated to:

- IRB
- IRB Chair/Vice Chairs
- IRB Administrators
- Researchers
- Others
- But Institution is Still Responsible

Institution Responsible For:

5. Appointing Qualified IRB Members
6. Supporting IRB Authority/ Decisions
7. Developing Policies/Procedures
8. Providing Education for IRB Members, Staff, & Research Personnel

Types of IRBs Examples

- Institutionally Based
- Independent
- Reciprocal/Affiliated (e.g. National Cancer Institute, Partners Health Care)

Institution Responsible For:

9. Ensuring Institution-wide Communication
10. Implementing Oversight Mechanism
11. Ensuring Assurances/Certifications/ Cooperating Performance Sites
12. Issuing Formal Reports to Regulatory Agencies

Institution: Examples

- Hospitals or Hospital Systems
- Academic Health Science Centers
- Universities
- Colleges
- Research Institutes

IRB Membership*: Establishing IRB

- At Least 5 Members
- Both Genders, If Possible
- Varied Professions
- Member with Nonscientific Concern
- Member with Scientific Concern
- Member Not Otherwise Affiliated with the Institution

*Administrator May Advise on Membership

IRB Membership

- Experience and Expertise
- Diversity of Backgrounds
- Sensitivity to Community Attitudes
- Knowledge of Institutional Commitments and Regulations, Applicable Law, Standards of Professional Conduct
- Knowledgeable & Experienced with Vulnerable Subjects
- Special Competencies of Ad Hoc Consultants

IRB Chair Responsibilities

1. Ensures IRBs Carry Out Their Regulatory Responsibility
   - Each Approved Protocol Meets All Requirements of 45 CFR 46 & if Applicable 21 CFR 50 & 56, 38 CFR Part 16
2. Conducts Exempt/Expedited Review or Delegates
3. Maintains Communication with Investigators, IRB Staff, & Signatory Official

IRB Chair Responsibilities (Cont.)

4. Provides Oversight & Leadership in Review of Alleged Noncompliance
5. Chairs Full Review Committee Meetings
6. Assists in Educating IRB & Researchers

IRB Authority

- Approve, Disapprove, or Modify Research
- Conducting Continuing Review
- Monitor Consent Process/Conduct of Research
- Suspend/Terminate Approval
- Investigate Allegations

IRB General Responsibilities

1. Ensure Rights, Safety, and Welfare of Human Research Subjects
2. Ensure Compliance with All Applicable Federal and State Laws/Regulations
3. Conduct Ethical Review of Human Research Activities Including Initial, Continuation, Modification, Unanticipated Problems, & Alleged Noncompliance

IRB Member Responsibilities

1. Conduct Protocol Review
2. Apply Disciplinary & Regulatory Knowledge
3. Attend Full Review Meetings
4. Avoid Conflicts of Interest
5. Propose & Develop IRB Policy
6. Complete Mandatory Education Requirements
7. Handle Allegations of Noncompliance
8. Maintain Confidentiality
9. Determine Whether Federal Reports are Required

Investigators/Research Personnel

1. Direct Responsibility for Ethical Conduct of Research with Each Human Subject
2. Design and Implement Ethical Research within Sound Study Designs According to the Belmont Ethical Principles and Standards of the Discipline
3. Involve Research Personnel Qualified by Training and Experience for Their Research Responsibilities

Investigators/Research Personnel (Cont.)

4. Obtain IRB Approval Prior to Initiating Human Research Activity
5. Comply with Federal and State Regulations, Institutional and IRB Requirements, and Requirements of the Health Insurance Portability and Accountability Act (HIPAA) Pertaining to Research
6. Implement Research as Approved and in Compliance with All IRB Decisions, Conditions, and Requirements

Investigators/Research Personnel (Cont.)

7. Maintain Appropriate Project and Personnel Oversight and Appropriately Delegate Research Responsibilities
8. Conduct Recruitment of Subjects Fairly and Equitably While Assessing Risks/Benefits to Research Subjects
9. Obtain and Document Informed Consent/Assent/ Authorization When Applicable
10. Provide a Mechanism for Receiving and Responding to Subjects' Complaints or Requests for Information

Investigators/Research Personnel (Cont.)

11. Monitor Data Integrity as well as the Rights, Safety, and Welfare of Human Subjects
12. Submit Progress Reports
13. Report Unanticipated Problems/Adverse Events
14. Obtain Prior Approval for Modifications to Research Protocols Including Promotional Materials
15. Maintain Written Documentation of Activities for Three Years After Completion

Sample Educational Documents PI Responsibilities

- A Principal Investigator's Guide to Responsibilities, Qualifications, Records and Documentation of Human Subjects Research
  http://www.research.uky.edu/ori/SOPs_Policies/9-PI_Responsibility_guidance-noDMS.pdf
- Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Drugs
  http://www.research.uky.edu/ori/human/44-Revised_IND_Document.pdf
- Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Devices
  http://www.research.uky.edu/ori/human/45-Revised_IDE_Document.pdf

IRB Administrator Responsibilities

1. Advising
2. Managing Protocol Review
3. Providing/Overseeing Education
4. Recordkeeping

IRB Administrator Responsibilities (Cont.)

5. Reporting
6. Developing Policies & Procedures
7. Handling Allegations & Complaints
8. Coordinating "Off-Site" Administrative Agreements

IRB Administrator Responsibilities (Cont.)

9. Conducting Quality Improvement or Assurance Reviews
10. Managing Staff & Infrastructure
11. Serving Liaison Function
12. Overseeing Special Initiatives (e.g., Obtaining & Maintaining Accreditation)