The Good, the Bad, the Ugly…We Feel Your Pain: A Review of the Intricacies of the IRB Application

Cheryl L. Byers, MHA, CIP
Director, Research Integrity & Compliance
USF
Overview of the IRB

**Function of the IRB**

The protection of rights, welfare and safety of human subjects through
- review
- approval
- continuing oversight

**Jurisdiction of the IRB** - All research activities involving human subjects
The Federal Regulations

- The Common Rule include (45 CFR 46 – Federal Regulations for the Protection of Human Subjects)

- The Food and Drug Administration (FDA) regulations governing human subjects research (21 CFR 56 – governing IRBs; 21 CFR 50 – governing Informed Consent)

- Health Insurance Portability and Accountability Act (HIPAA) 45 CFR 160 and 164
The Belmont Report

- Ethical yardstick for the protection of human subjects who participate in research

- Three main principles:
  - Respect for Persons
  - Beneficence
  - Justice
The Good, the Bad, and the Ugly....How do I complete this application??!!
Study Team Members

- Principal Investigator (PI) – the individual responsible for the oversight of all study activities

- Co-Investigators – individuals who assist with study procedures, can assist in the absence of the PI, etc.

- Study Coordinator - maintains regulatory file, may consent subjects, execute study procedures, etc.

- Key Personnel – anyone who will be working on the project who will consent individuals, access data, execute study procedures, etc.

- Individuals participating in the research who are not affiliated with USF or USF Affiliates should not be included in the application
Study Description

- Be brief!

- Provide an overview of the study in lay terms
  - Keep in mind that the IRB has community members and non-scientist who need to be able to understand what the study is about.

- This information will be included on the home page of the application.
Human Subjects Protection

Education

- All personnel included on an IRB application must comply with the HRPP Policy 711.

- Certification is valid for 2 years.

- The application will display study team members whose education has expired.

- Applications can be processed while education is being obtained – the application will not be approved until all study team members have current education in the protection of human subjects.
**Human Subjects Research Determinations**

**Research** is defined as:

A systematic investigation designed to develop or contribute to generalizable knowledge.

**A Human Subject** is defined as:

- A living individual about whom an investigator obtains data through intervention or interaction or obtains identifiable private information.
Funding Source

- It is important that you select a funding source for your study.

- Studies funded by for-profit entities will display a page for invoicing for IRB fees.

- Studies funded by grants must include the grant document.
  - OHRP expects the IRB to compare the grant document to the proposal submitted to the IRB to ensure consistency between the documents.
  - Multiple studies can be submitted for one grant.
Study Location

- Select the USF site or Affiliate site where the study will be conducted.

- Applications for studies conducted at off-site locations or those not affiliated with the University must include a letter of support.

- International studies must include documentation from the local site approving the conduct of the research.

- See USF HRPP Policies 304 and 709 for more information regarding Transnational Research and Off-Site Research respectively.
IRB Review/Research Type

- Review Type
  - Exempt
  - Expedited
  - Full Board

- Research Types
  - Biomedical Research
  - Social & Behavioral Research
  - Record Review/Tissue Analysis
IRB Review and Approval

Exempt

- Minimal Risk research only.
- 6 categories of review.
- At USF, only the IRB can determine that a study is exempt.
- Approval is valid for 5 years.
- Should you wish to continue the conduct of the research after the 5 year period, a new application must be submitted for review.
IRB Review and Approval

Expedited Review

- Does not mean “Fast!” in the regulations!
- Minimal Risk research only.
- Determination made by IRB Chair or their designee
- The study must meet one of the nine approved categories for review.
- Expedited studies are approved for one year at which time applications for continuation or closure must occur.
- Retrospective chart reviews are processed as expedited category 5.
IRB Review and Approval

Review by Full IRB

- Conducted at a convened meeting.
- Primary reviewer system is utilized.
- Must have a majority of members present including at least one member who is a non-scientist.

IRB actions

- Approve
- Approve contingent upon response to minor concerns
- Defer
- Disapprove
IRB Review and Approval

- Amendments or any change in the protocol, consent form or other study documents.
  - These changes cannot be implemented prior to USF IRB approval unless it is to maintain the safety of subjects.
- Unanticipated Problems involving risks to subjects and others (including all harms).
- Deviations or Variations from the approved protocol.
- Continuing Review of ongoing research studies.
  - All approved research is subject to continuing review; approval is for up to one year, may be less depending on level of risk.
To Review HSR, the following is needed

- Your protocol or study plan (template available on ARC).
- Your informed consent document (template available on ARC).
- Your grant application.
- All recruitment material.
- Any surveys, questionnaires, focus group questions, etc. which may be used in the study.
To Review HSR, the following is needed continued...

- If study involves deception, your de-briefing statement.

- Your data collection form for retrospective review of medical records.

- Letter from the FDA that includes your Investigational New Drug (IND) number for studies using investigational drugs.

- IND exemption letter.

- Investigational Device Exemption (IDE) number.
IRB Documents Required for Review

- Surveys/Questionnaires
- Interview Scripts
- Focus Group Questions
- Psychological/Neuropsychological Testing
Study Population

- Inclusion/Exclusion Criteria – copy/paste from protocol/research plan

- Age of participants – very important to include!

- Recruitment
  - Seen as the initial stage of the informed consent process.
  - How will you recruit subjects?
  - If utilizing flyers, posters, brochures, IRB approval is required.
  - How will you ensure privacy during this procedure?
  - How will you ensure the subject has sufficient time to review the informed consent document?
Study Population Continued

- Number of subjects requested to enroll in your research study should include the number of individuals who will sign the informed consent document.
  - Consider screen failures
  - Consider drop outs
  - Consider transfers
  - Consider withdrawals

- Studies can always be amended to increase the number of subjects to enroll/consent.
Vulnerable Populations

- Per the federal regulations:
  - Women and their fetus
  - Prisoners
  - Children

- Other vulnerable populations:
  - Certain ethnic or racial groups
  - Cognitively impaired
  - The elderly
  - Individuals who do not speak English
  - Socially or economically disadvantaged
Ethnic and Racial Categories

- In order to ensure we are meeting the ethical principle of justice, the IRB must consider the ethnic and racial diversity of the subject population being recruited.

- The IRB will request this information if you are prospectively enrolling research subjects.

- If you are conducting surveys and certain other research, you are not required to collect information regarding ethnicity, race, and gender.
Informed Consent: Not Just a Document

- Founded in the principle Respect for Persons, informed consent involves the ongoing, active exchange of information between the subject and the investigator (and/or the study team).

- Ensures
  - The subject understands what they are being asked to do.
  - The subject has the opportunity to ask questions.
  - The person truly wants to continue in the study.
Informed Consent – The Basic Requirements

- The study involves research
- The purpose of the research
- Expected duration of participation
- Procedures which will take place
- Notation of procedures which are experimental
- Alternatives to participation
Informed Consent– The Basic Requirements

- Any potential risks or discomforts
  - Physical, emotional and/or psychological
  - Risks to a person’s ability to obtain or retain employment or insurance, or to face civil or criminal action

- Potential benefits to subject or others
  - Do not overstate benefits
  - If there are no benefits to the subject, say so

- The extent to which confidentiality will be maintained

- For studies involving more than minimal risk, a statement of any medical treatment that may be provided for research related injuries
Informed Consent– The Basic Requirements

- Who to call for research related questions, their rights as research subjects, or if there is a research related injury

- A statement that participation is voluntary and withdrawal from the study can occur at any time without penalty or loss of benefits
Informed Consent: Additional Elements

- Any unforeseen risks to participation
- Circumstances that necessitate the subjects to be terminated from participating in the study
- Additional costs associated with their participation
- Number of subjects participating at the local site as well as those participating at all sites
- Consequences for early withdrawal from the study
- A statement regarding new findings that may affect their willingness to continue participating
There are times when the process of informed consent can be waived:

- The study poses no greater than minimal risk
- The waiver will not adversely affect the rights of the subjects
- It is not practicable to obtain informed consent
- When appropriate, the subject should be provided with pertinent information after participation

Each of the questions above requires a separate and appropriate answer.

This waiver is typically used for studies involving retrospective chart reviews.
Can Documentation Be Waived?

- Waiver of signed consent can take place under the following circumstances:
  - The only record linking the subject and the research would be the consent document and the principle risk would be the potential harm resulting in a breach in confidentiality. Each subject should be asked if they want a record linking them to the research and their wishes will govern the process.
  - The research presents no more than minimal risk of harm and involves no procedures for which written consent is normally required outside the research context.
Compensation & Cost

- **Compensation**
  - Study teams must include the amount of compensation (if any) which will be provided to subjects. This includes:
    - Compensation for participation on a per visit basis and total compensation.
    - Compensation for transportation, meals, or any other expenses.
  - The IRB must ensure the amount of compensation will not unduly influence participation in the research study.

- **Cost**
  - What is standard of care which will be billed to insurance?
  - What are costs of participation in the research incurred by the subject?
Risks to Subjects

- The IRB is required by regulation to consider all risks to subjects.
- The ethical principle beneficence speaks to minimizing harms and maximizing the benefits to participation.
- All risks to participation should be outlined in the IRB application.
- Early stopping criteria must also be included for research involving drugs and devices.
Benefits to Participation and Alternatives

- The IRB must consider all benefits to participating in the research in relation to the risks.

- Beneficence tells us that we should maximize the benefits of research while minimizing the harms.

- Compensation is not a benefit to participating in research.

- Any alternatives should be outlined in both the application and informed consent document including the alternative to not participate.
Privacy and Confidentiality

- **Privacy**: The right one has to control the extent, timing, and circumstances for sharing information about oneself with other individuals.

- **Confidentiality**: The treatment of information/records/data that one has disclosed in a relationship of trust with the expectation that it will not be divulged to anyone without permission and in ways that are consistent with the understanding of the original USF disclosure.
Privacy and Confidentiality Continued…

- Investigators are expected to outline in their IRB applications how they will maintain the privacy of the subject and confidentiality of the data throughout the research project.

- This includes documentation such as:
  - Study files will be kept in a locked file cabinet in a locked room.
  - Data will be maintained in an electronic data capture system which is maintained on a computer which is password protected and on a secure server. Only study personnel will have access to the electronic data capture system.
Data and Safety Monitoring Plan

- All studies, regardless of risk, should include a data and safety monitoring plan.

- DSMPs are designed to ensure that studies involving human subjects have a system for appropriate oversight and monitoring of the conduct of the research and integrity of the data.

- See USF HRPP Policy 803 for additional information on DSMPs.
Data and Safety Monitoring Boards

- A DSMB is an independent group of individuals with pertinent expertise that reviews, on a regular basis, accumulating unblinded data from protocols involving human subjects research to assure the continuing safety of research subjects, relevance of the study question, appropriateness of the study, and integrity of the accumulating data.

- Review of this data help the DSMB determine whether or not the trial should continue, be modified, etc.

- The NIH requires the establishment of DSMBs is required for all Phase III multicenter clinical trials involving interventions that entail potential risk to the participants.
Research Involving Drugs

- **Drug**: “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” and "articles (other than food) intended to affect the structure or any function of the body of man or other animals.”

- An IND is required whenever a research study uses a drug that has not received FDA marketing approval.

- An IND may be required for a drug that is FDA approved if the research proposes a use of the drug that was not included in the existing FDA approval unless the research meets FDA’s criteria for an exemption from the IND regulations.
The USF IRB expects applications submitted for review of investigational drugs include a letter from the FDA outlining the IND number or a letter from the FDA noting the exemption.

Investigators Brochures (IB) must be submitted for all investigational drug applications.

ICF must outline the investigational nature of the study including the fact that the drug is not FDA approved (or approved for the use/purpose of the study).
Exemption from IND Requirements

- Clinical investigations of a drug that is lawfully marketed in the US is exempt if all the following apply:
  - The study is not intended to support FDA approval of a new indication or a significant change in the product labeling;
  - The study is not intended to support a significant change in the advertising for the product; and
  - The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
  - The study is conducted in compliance with IRB and informed consent regulations set forth in 21 CFR parts 56 and 50; and
  - The study is conducted in compliance with 21 CFR 312.7 (promotion and charging for investigational drugs).
A device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is:

- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or

- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.
The IRB determines whether a device is a Significant Risk Device or a Non-Significant Risk Device

See USF HRPP Policy 403 for more information about the use of Devices in Clinical Trials
Dual Enrollment

- If you are recruiting individuals who are enrolled in an ongoing research protocol, you will need to outline this in your application.

- Approval by the PI of the other study/studies must be documented in the application.

- Investigators should consider the burden on research subjects when making the decision to enroll individuals participating in other research protocols.
Research Requiring Review by USF IRB and USF Biosafety Committee

- Infectious Agents
- Regulated Toxins
- Recombinant DNA
- Gene Transfer
- Recombinant DNA Vaccine
- Xenotransplantation
Research Involving Radiation Above Standard of Care

- If your research study involves the use of radiation above the standard of care, you must have approval by:
  - The Radiation Safety Committee for MCC studies. Documentation should be uploaded in the USF IRB application.
  - The Radiation Safety Officer for all other studies – the USF IRB staff will route the application to the RSO for review and approval.

- The ICD should contain information regarding whether or not radiation above SOC is involved.

- The ICD should also outline how much radiation the study involves in lay terms.
When to Submit Applications

- Upon notice of award/JIT information receipt
- At least 30 days prior to the date in which you need to conduct the research
- If going abroad, working with the public school system or when any external factor is involved, give yourself at least 45 days
Submitting Amendments

- Any change to your IRB application/study must be submitted to the USF IRB for review and approval prior to the implementation of the change.

- Amendments can be reviewed by expedited procedures or by the convened IRB depending upon the nature of the change.

- Only one amendment can be submitted at one time.

- Multiple changes can be included on one amendment.
Submitting Continuing Review Applications

- CR applications must be submitted at least 45 days prior to the study expiration date to ensure continued approval of the research.

- You cannot have a CR pending and submit an amendment or vice versa.

- You can convert “paper” studies into eIRB at CR or before. If converting at CR, please submit 60 days prior to review.

- All “paper” studies must be electronic by December 31, 2012.
Submitting Reportable Events

- Reportable Events Include:
  - Unanticipated Problems
  - Deviations
  - Complaints/Concerns
  - Noncompliance
  - Breach in Confidentiality
  - Other
Questions?