PRINCIPAL INVESTIGATOR RESPONSIBILITIES AND STUDY DOCUMENTATION 2

Principal Investigator Responsibilities and Study Documentation

1 Goals

Upon completion of this module, the learner will be able to:

- Describe the responsibilities of the principal investigator as they relate to study conduct and compliance with federal and institutional regulations.
- Describe the necessary interactions of the principal investigator with the sponsor and regulatory bodies.
- Identify the principal investigator's responsibilities for the protection of human research subjects
- Review proper methods of documentation of study activities to reflect compliance with federal and institutional policies

2 Introduction

The principal investigator of a human subject research study is ultimately responsible for the conduct and documentation of all study activities and for assuring compliance with federal regulations and IRB policies.

Even though a principal investigator (PI) may delegate specific tasks to other members of the research team, he or she cannot delegate the responsibility for ensuring that those tasks are completed in accordance with institutional and federal regulations.
The following pages of this chapter discuss specific investigator responsibilities although all topics listed may not apply to the design of every study, e.g., drug accountability.

3 Regulations

The principal investigator must acknowledge and accept the responsibility for protecting the rights and welfare of human research subjects and must know and comply with current Federal regulations and IRB requirements governing human subject research.

The regulations governing the responsibilities of the University of Pittsburgh investigators conducting human subject research include but are not limited to:

- **The University of Pittsburgh's Federalwide Assurance Agreement (FWA) with the Office of Human Research Protection (OHRP).**

With this agreement, the University commits to following the Federal Policy regulations (Title 45 Part 46) for protecting human subjects in research.

- **The FDA regulations governing human subject protections and good clinical practices for studies involving investigational drugs, devices and biologics.**

  The specific regulations concerning investigator responsibilities are as follows:

  - Investigational drugs -- 21 CFR 312.60
  - Investigational devices - 21 CFR 812.100
  - Biologics - 21 CFR 600.10

When conducting research that involves a product that is regulated by the FDA, investigators must sign an agreement indicating that they accept their responsibilities (e.g., Form 1572 for investigational new drugs and biologics and an "Investigator's Agreement" for devices).

The IRB Reference Manual serves as guidance in complying with the above regulations. www.irb.pitt.edu. Additional guidance and resources for investigators may also be obtained through the Office of Clinical Research website http://www.clinicalresearch.pitt.edu/irs/resources/index.cfm

- **Regulations concerning financial disclosure can be found in** 21 CFR 54.

4 Protocol

The principal investigator must conduct a research study in accordance with the current IRB-approved protocol and consent form.

When the IRB approves a protocol or modification submission, it is mandatory that the protocol is implemented exactly as written.

The principal investigator must not institute any changes to the IRB-approved protocol and/or consent form document without first obtaining written IRB approval for such changes. The only exception to this requirement is a change in procedure that may be necessary to eliminate an apparent immediate hazard to a given research subject. The sponsor must also be notified of an investigator's intent to modify the protocol or consent form.

If an unplanned protocol deviation or violation occurs, the investigator must notify the IRB Chair and the sponsor to describe the occurrence. All protocol deviations or violations that involve risks to human subjects or others must be reported to the IRB as an unanticipated problem. (Discussed further in Section 5.10.)

5 Study Supervision

The principal investigator must personally conduct or supervise the study.

The principal investigator must provide all co-investigators and research study staff with the most current information (i.e., protocol, consent forms, regulatory changes) to ensure proper study conduct at all times.

Principal investigators must also ensure that collaborating investigators located at other institutions obtain proper IRB approval for the study. For federally funded studies conducted at outside institutions, the PI must also ensure that those institutions have assurance agreements with the Office for Human Research Protections. Even though a collaborating physician may never see a study participant, the protection of human subjects extends to an off-site investigator who is playing a role in the study that allows him or her access to study data (such as evaluating tissue samples).

6 Recruitment

The principal investigator must recruit subjects in an ethical manner by respecting the research subjects' privacy and the confidentiality of their personal health information.

Investigators may inform their own patients about their studies because the investigators, as clinicians, have the right to access their patients' personal information that may indicate if the patients are potential subjects. In all other instances, such as with patients of other caregivers or in other practices, an investigator cannot directly access private information or contact these individuals directly.

This same principle holds true regarding investigator access to the names or confidential information of members of any community, work, school, trade, or union-based program.

Not adhering to this practice is considered to be "cold-calling," which is prohibited by the Office of Human Research Protections.

Cold-calling is the initiation of contact with the subject by investigators or research staff who are not familiar with the potential research subject, based on knowledge of confidential information regarding the subject (e.g., medical record information) without prior introduction of the research project and investigators to the subject.

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule places specific limitations on researchers' access and the use of personal health information of potential subjects.

Under HIPAA, in order for an investigator to contact individuals who may be eligible for a study, the patients would:

- Have to be patients of that investigator, or
- Have previously signed a consent form for an IRB-approved research registry that allows contact, or
- Be willing to sign an authorization for their physician to provide the investigator with their health information.

7 Informed Consent

The principal investigator must ensure that the requirements for obtaining informed consent are met prior to the initiation of any study procedures.

It is the investigator's responsibility to oversee the informed consent process, making sure that each potential subject fully understands the purpose of the research, the research procedures, the potential risks of study participation, and his or her rights as a research study volunteer.

For more information on the informed consent process, please see the module dedicated to “Informed Consent.”

8 Enrollment

The principal investigator must ensure that participant enrollment is done in accordance with the guidelines outlined in the IRB Reference Manual.

The principal investigator must have written approval from the IRB prior to the enrollment of subjects. Every subject (or legally authorized representative) must provide written informed consent prior to ANY research procedure (unless a waiver has been granted by the IRB).

Also, the principal investigator must cease enrollment :

- If IRB approval has lapsed
- If the protocol is suspended (by the IRB or sponsor)
- Following termination of IRB approval of the research study or termination of enrollment by the sponsor or by the principal investigator.

9 Record-Keeping

The principal investigator must maintain adequate, current and accurate records that document all observations and other data pertinent to the involvement of each research subject.

Research records should be maintained in a manner whereby an individual not associated with the conduct of the study (monitor, auditor) can easily track the course of a subject’s involvement.

There should be records that document:

- That the subject met the eligibility criteria (inclusion as well as exclusion)
- The informed consent “process” in addition to the signed consent document
- That all screening procedures were completed per protocol (and the results)

- That all study procedures were completed per protocol (and the results)
- Accountability of all study devices/medications (if applicable)
- The status of each subject following any procedure that involves risk, discomfort or emotional anxiety
- Adverse events as well as treatment, interventions and outcome of the event
- All deviations from the IRB approved protocol
- The circumstances of the subject's study completion or termination of involvement

The original documents where observations, test results or activities pertaining to a subject are first recorded are called **source documents**. All source documents (e.g., lab results, EKG reports, physician progress notes, or a scrap of paper with vital signs or notes) must be retained. Information from the source documents are then frequently transcribed onto **case report forms** designed by the sponsor company or the principal investigator to track study activity in a standard format. Should any discrepancies of documentation occur, the source document is always considered the correct data.

In some instances, information such as vital signs, height and weight, may be documented directly onto a case report form. The case report form then becomes the source document.

For their own protection and the protection of the study participants, it is important that investigators maintain accurate and complete documentation of all test articles (drugs, devices, biologics). These records should include:

- records of receipt including quantity and lot numbers
- dispensing records including subject ID, date and amount or article dispensed
- return records including date and amount returned or retrieved
- compliance records
- disposition of excess or returned articles

The IDS (Investigational Drug Service) is available (for a fee) to maintain drug accountability for applicable studies. If the principal investigator chooses to maintain his/her own system of test article accountability, appropriate measures must be in place for storing and maintaining security of the articles. The IDS must be notified of all studies that involve the use of medications and has the authority for oversight of storage and usage.

If an error is made when completing a research form or record, it must be corrected without obscuring the original data entry. The correct method is to put a single line through the incorrect entry and write the correction beside it. All corrections must be initialed and dated by the individual making the correction. White-out should NEVER be used to correct research documentation.

Confidentiality of all subject records must be maintained. Records must be kept in locked cabinets in locked rooms/suites. Identifiable subject records should be kept separate from records with ID codes or unique study numbers. The "link" of study

records to the subject should be kept in a secure location, separate from the research records. Computerized records must be password protected with limited access.

In addition to subject records, the principal investigator must maintain regulatory records. Sponsored trials typically provide binders to retain the records in a particular manner. However, all investigators should maintain regulatory files in a systematic and organized manner.

The **regulatory file** includes but is not limited to the following items. The most common documents are indicated in bold. The remaining items would be included if applicable to study design.

- **Protocol** (all versions in chronological order)
- **Informed consent document** (all versions in chronological order)
- **Investigator's CVs**
- **IRB correspondence** (all submissions, IRB comments and PI responses in chronological order)
- **Sponsor correspondence**
- **Signature list of research staff** (and responsibilities)
- **Serious adverse event reports**
- **Monitor visit log and corresponding monitor reports**
- **Reports of local Data Safety and Monitoring Boards**
- **Final study report**
- Laboratory certification
- Range of normal laboratory values
- Reports of sponsor Data Safety and Monitoring Boards
- Drug accountability documentation
- Certifications for relevant training/education
- Investigator's Brochure
- Form FDA 1572 (or Investigator's Agreement)

All research records must be retained for certain periods of time which may vary by regulatory body. As a general rule, the University of Pittsburgh IRB requires that records be kept for a minimum of five years following study completion or discontinuation or upon written notification from the sponsor that the files may be destroyed, whichever comes last.

10 Adverse Events

The principal investigator must ensure that subjects who have suffered an adverse event associated with research participation receive adequate care to correct or alleviate the consequences of the adverse event.

An **adverse event** is any untoward medical occurrence that might present itself during administration or application of a research intervention and which may or may not have a causal relationship with the research intervention. In addition to providing care and

oversight of the treatment of an adverse event, the event must be properly documented and reported.

Investigators must record all adverse events, regardless of severity and causality, in the subject's research record and on the data collection forms for sponsored trials.

If the event is considered serious, unexpected and related to the research intervention, it must be reported to the IRB.

- A **serious adverse event** is an event that is fatal or life-threatening, requires or prolongs hospitalization, produces a disability, or results in a congenital anomaly or birth defect.

- An **unexpected** event is not identified by nature, severity or frequency in the current University approved protocol or consent document.

- A **related** event means that there is a reasonable possibility that the adverse event might have been caused by the research intervention, i.e., a causal relationship between the adverse event and the research intervention cannot be ruled out by the investigator.

Note that an **internal adverse event** is an event that occurs at the University of Pittsburgh, UPMC, or other site that falls directly under the authority of the University IRB.

An **external adverse event** is an event that occurs at a site external to the authority of the University of Pittsburgh IRB and is reported to the University or UPMC investigator.

The following table summarizes the requirements and deadlines for reporting to the IRB adverse events or unanticipated problems (See Section 5.10) involving risks to human subjects or others.

Event Criteria (must meet all)	Reporting Deadline
Internal adverse event that is: • Unexpected, • Fatal or life-threatening, and • Related to the research intervention	Within 24 hours
Internal adverse event that is: • Unexpected, • Serious (but not fatal or life-threatening), and • Related to the research intervention	Within 10 working days

External adverse event that is: • Unexpected, • Serious, and • Related to the research intervention	Within 30 working days
All other unanticipated problems involving risks to human subjects or others	As soon as possible

Details of the required documentation and submission requirements can be found in Chapter 3 of the IRB Reference Manual. The Adverse Event Report Form is available at www.irb.pitt.edu.

Some additional points regarding reporting adverse events are as follows:

- For gene transfer interventions, there are additional reporting requirements to the Biosafety (rDNA) Committee, NIH Office of Biotechnology Activities (OBA), and the FDA.
- The sponsor of a drug, device or biologic study is responsible for notifying the FDA of adverse events. Therefore, when an investigator also acts as the sponsor, the investigator assumes the responsibility for directly notifying the FDA of adverse events.
- Adverse events occurring in UPMC facilities may also need to be reported to Risk Management through the Risk Master program. See the adverse event reporting policies for the specific UPMC hospitals at http://infonet.upmc.com/Default.htm.

11 Unanticipated Problems/Events

The principal investigator must provide reports as required by the sponsor and by the IRB.

As the study progresses, the principal investigator is required to submit reports on the progress and problems associated with study conduct to the IRB as well as the study sponsor.

In addition to reporting of adverse events as they occur, the investigator must also report deviations from the protocol and **unanticipated problems involving risks to human subjects or others.**

These problems include, but are not limited to such occurrences as:

- Any incident or unintentional deviation from the IRB-approved protocol that involves risk or has the potential to recur. For example:
  - Missed study visit that involves safety monitoring

- Lost or stolen research records containing identifiable subject information

- Any deviation from the protocol done without prior IRB review to eliminate an apparent immediate hazard to a given research subject
  (Example - slowing rate of infusion of IV medication specified in protocol in response to subject's discomfort or pain during more rapid infusion)

- Any complaint of a subject that presents an unanticipated risk or which cannot be resolved by the research staff
  (Example - spouse of research subject demanding research records)

Forms and instruction for reporting unanticipated problems may be found at the IRB website www.irb.pitt.edu.

12 Data and Safety Monitoring Plan/Board

For the safety of subjects, all research must have a method in place to regularly monitor study activity and accumulated data. The IRB requires that all protocols include a description of how this oversight activity will be implemented at the local level as well as the sponsor level (or central level) if applicable. The plan should include:

- Who will be responsible for monitoring the activity and data

- What will be monitored

  - Cumulative adverse event information including causality and frequency
  - Confidentiality of information or breach of confidentiality
  - Relevant information that might impact the safety of the study participants (e.g., results of related studies)
  - Conclusions and decisions regarding risk/benefit ratio and whether the study may continue, requires modification or should be terminated.

- The frequency of review and or monitoring meetings

The investigator is required to implement this plan as written and submit reports to the IRB at the time of study renewal.

Please see Appendix L of the IRB Reference Manual for more details.

13 Inspections

The principal investigator must make records available for inspection.

Investigators are required to make research records available for audit by the:

- Sponsor or its representatives

- FDA
- OHRP
- Institutional oversight committees (e.g., the University of Pittsburgh's Research Conduct and Compliance Office or UPMC Corporate Compliance).

The investigator must also notify the IRB of any upcoming FDA inspections or audits.

14 New Information

The principal investigator must ensure that research subjects are kept fully informed of any new information that may affect their willingness to continue to participate in the study.

New information is usually presented to subjects during a discussion which is viewed as a continuation of the informed consent "process." The information is also prepared in written form as an addendum to the consent document (for previously enrolled subjects) or in a revised version of the informed consent document for future enrollment. Revised consent documents and addenda must be submitted to the IRB and approved prior to implementation. (See Chapter on Informed Consent).

15 Accountability of Investigational Agents

The principal investigator must ensure accountability of investigational drugs, devices or biologics.

Accountability of investigational products is the responsibility of the investigator. As mentioned previously, maintaining accurate records is vital. Investigators may delegate some of the management responsibilities to an appropriate institutional entity (e.g., investigational drug service).

16 Conflict Of Interest

The principal investigator must disclose to the sponsor and to the IRB any potential conflict of interest, including:

- Any equity interest in the entity that either sponsors the research or owns the technology being evaluated that exceeds 5% ownership interest or a current value of $10,000.
- Receipt of salary, royalty, or other payments from the entity that either sponsors the research or owns the technology being evaluated that is expected to exceed $10,000 per year.
- Possession of an agreement with the University or an external entity that would entitle sharing current or future commercial proceeds related to the technology

being evaluated (e.g., royalties through a license agreement).

- Existence of a personal relationship with a start-up company (which is being monitored by the Entrepreneurial Oversight Committee) that has an option or license to utilize the technology being evaluated.

Please be aware that having a significant personal financial interest in the study sponsor or the technology being evaluated will generally disqualify a person from being the principal investigator.

Please note that Module 1, Research Integrity, Chapter 4, and Module 4 are dedicated to the Conflict of Interest issue.

17 Financial Disclosure

The principal investigator must assume the responsibility for procuring significant financial interest disclosures from co-investigators and other study personnel and devise and implement a plan to eliminate, minimize and/or manage potential conflicts of interest.

If applicable, the principal investigator must devise a management plan that must be approved by the IRB.

Specific institutional policies governing conflict of interest can be found on the University's Conflict of Interest Office's website at http://www.rcco.pitt.edu/coi/ and are also addressed in Module 4.