BASIC INSTITUTIONAL REVIEW BOARD (IRB) REGULATIONS AND REVIEW PROCESS 2

Basic Institutional Review Board (IRB) Regulations and Review Process

1 Introduction

The purpose of this module is to provide a basic understanding of the human subject protection regulations that govern the participation of human volunteers in research in the United States. By end of the module you will be able to:

- Describe the role, authority, and composition of the IRB.
- List the IRB requirements for conducting research involving human subjects.
- Describe the types of IRB review.
- Describe the process of working with the IRB.
- Identify other regulations and regulatory groups that require compliance based on the type of research being conducted.

2 IRB Role, Authority, and Composition

2.1 The Role of the IRB

An Institutional Review Board (IRB) is a review committee established to help protect the rights and welfare of human research subjects. Regulations require IRB review and approval for ***research involving human subjects*** if it is funded or regulated by the federal government. Most research institutions, professional organizations, and scholarly journals apply the same requirements to all human research. Although federal regulations refer to IRBs, an institution may have chosen a different name for this committee.

To clarify when IRB review is required, let's define some terms:

- **Research:** Federal regulations define research as: "a systematic investigation designed to develop or contribute to generalizable knowledge." [45 CFR 46.102(d)] If an investigator is unclear about whether a planned activity is research, the investigator should contact his/her IRB office.
- **Human Subjects:** The Department of Health and Human Services (DHHS) regulations define a human subject as "a living individual about whom an investigator (whether professional or student) conducting research obtains:

- Data through intervention or interaction with the individual.
  Or

- Identifiable private information." [45 CFR 46.102 (f)]

  Note: Some state laws include deceased individuals and fetal materials as "human subjects." Check with the local IRB about the definition of a human subject that applies in the state where the research will be conducted.

- **Private Information** includes:
  - Information about behavior that occurs in a setting in which the individual can reasonably expect that no observation or recording is taking place.
  - And information that has been provided for specific purposes, other than research, where the individual can reasonably expect that it will not be made public (e.g., a medical record.) [45 CFR 46.102(f)].

- **Coded Private Information or Biological Specimens.**
  DHHS Office of Human Research Protection (OHRP) policy considers private information or specimens to be individually identifiable when they can be linked to specific individuals either directly or indirectly through coding systems. DHHS OHRP guidance states that only a knowledgeable person or entity is authorized to determine if coded specimen or data constitute research. An investigator cannot make that determination. [OHRP DHHS Guidance on Research Involving Coded Private Information of Biological Specimens, August 2004.]

- **Clinical Investigation**: The Food and Drug Administration (FDA) defines clinical investigation as "any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration, or is not subject to requirements for prior submission to the Food and Drug Administration, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit." [21 CFR 56.102(c)]

2.2 The Authority of the IRB

Federal regulations stipulate that an IRB can:

- Approve research.
- Disapprove research.
- Modify research.

- Conduct continuing reviews.
- Observe / verify changes.
- Suspend or terminate approval.
- Observe the consent process and the research procedures.

2.3 The Composition of the IRB

Federal regulations dictate that the IRB membership will include:

- At least five members.
- Member of both sexes.
- Members that come from varied professions.
- At least one member whose primary concerns are in nonscientific areas.
- At least one member whose primary concerns are in scientific areas.
- At least one member who is not otherwise affiliated with the institution.

The regulations also stipulate that the IRB membership will include:

- Reviewers with experience and expertise in all of the areas of research being reviewed. At its discretion, an IRB may 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.
- Diversity of backgrounds.
- Sensitivity to community attitudes.
- Knowledge of institutional commitments and regulations, applicable laws, and standards of professional conduct.
- Knowledge and experience with vulnerable populations.

Note: If an IRB reviews research that involves vulnerable subjects, the IRB must consider the inclusion of an individual who has knowledge of, and experience with, these vulnerable subjects. The regulations may also require a voting IRB member who has relevant research expertise (for example, research involving prisoners). IRBs may call experts to help with problematic reviews, but those persons may not vote on the disposition of the application. If an IRB member has a conflict of interest, that member cannot be present for the review of that project except to provide the IRB with information as requested and may not vote on that project.

3 IRB Requirements for Human Subjects Research

3.1 IRB Requirements

Institutions and IRBs vary in the practices that assure they meet the federal regulations and in the details of the standards they apply. What follows are the *minimum* federal requirements. Institutions and/or IRBs may add additional protections or procedures to these minimum requirements.

IRB applications usually contain, at a minimum, information that allows IRB members to assess:

- **Risk / anticipated benefit analysis.**
  - Identification and assessment of risks and anticipated benefits.
  - Determination that risks are minimized.
  - Determination that risks are reasonable in relation to potential benefits.

- **Informed consent.**
  - Informed consent process and documentation.

- **Assent.** The affirmative agreement of a minor or decisionally impaired individual to participate in research.
  - Assent process and documentation.

- **Selection of subjects.**
  - Equitable selection in terms of gender, race, ethnicity.
  - Benefits are distributed fairly among the community's populations.
  - Additional safeguards are provided for vulnerable populations susceptible to pressure to participate.

- **Safeguards** that ensure that subject recruitment does not invade individuals' privacy and that procedures are in place to assure that the confidentiality of the information, collected during the research, is monitored.

- **Research plan for collection, storage, and analysis of data.**
  - Clinical research studies often include data safety monitoring plans and/or data safety monitoring boards (DSMB). IRBs will review the plans to ensure they are adequate to protect human subjects.

- **Research design / methods** that are appropriate, scientifically valid and therefore, justify exposing subjects to research risks.

- **Additional information about identification**, recruitment and safeguards if the research involves special populations.

- **In addition, the IRB must review:**
  - The qualifications of the principal investigator (PI) and scientific collaborators.
  - A complete description of the proposed research.
  - Provisions for the adequate protection of rights and welfare of subjects.
  - Compliance with pertinent federal and state laws/regulations and institutional policy.

3.2 Responsibilities of the Principal Investigators and Research Staff

Principal investigators and research staff have specific responsibilities. They are required to:

- Protect the rights and welfare of human subjects who participate in research.
- Understand the ethical standards and regulatory requirements governing research activities with human subjects.
- Inform research staff of the regulations governing research and the institutional research policies.
- Ensure that all research activities have IRB approval and other approvals required by the institution before human subjects are involved.
- Implement the research activity as it was approved by the IRB.
- Obtain the informed consent of subjects before the subject is involved in the research and document consent as approved by the IRB.
- Maintain written records of IRB reviews and decisions and obtain and keep documented evidence of informed consent of the subjects or their legally authorized representative.
- Obtain IRB approval for any proposed change to the research protocol prior to it's implementation.
- Comply with the IRB requirements for timely reporting of unanticipated problems involving risks to subjects or others including adverse events, safety reports received from the sponsor, or data safety and monitoring summary reports.
- Obtain continuation approval from the IRB on the schedule prescribed by the IRB.
- Make provisions for the secured retention of complete research records and all research materials.
- Ensure the confidentiality and security of all information obtained from and about human subjects.

- Verify that IRB approval has been obtained from all participating institutions in collaborative activities with other institutions.

- Notify the IRB regarding the emergency use of an investigational drug or device within 5 working days of the administration of the test article.

3.3 If IRB regulations are not followed, consequences could include:

- Suspension of research project.

- Suspension of all of a PI's research projects.

- Inability to use data or publish results.

- Notification of sponsors, regulatory agencies and funding agencies of noncompliance.

- Debarment by FDA from using investigational products.

- Inability to receive funding from federal grants.

- Additional monitoring and oversight by the IRB and/or third party monitoring of research activities.

- Termination of employment.

- Loss of licenses.

- Immediate shut-down of ALL research at an organization.

3.4 Consequences of Not Following IRB Regulations

These are not theoretical consequences. Some or all of these consequences have occurred at sites where human subjects research was conducted improperly or without IRB approval.

4 The Types of IRB Review

Contact the IRB office for the guidelines for submitting an IRB application. The IRB will provide guidance in implementing federal regulations. The IRB can be a resource for investigators and staff. Under federal regulations, there are three possible IRB review procedures:

1. **Full Committee Review.**

2. **Expedited Review.**

3. **Review for Exemption Status.**

4.1 Full Committee Review

Full committee review is the standard type of review described in the Federal regulations. It must be used for the initial review of all studies that are not eligible for expedited review or exemption status. The procedures and conditions for **full committee review** require that:

- The review must be conducted at a convened meeting of the IRB. A majority of IRB members (a quorum) must be present at the meeting.
- At least one member whose primary concerns are in nonscientific areas must be present at the meeting (in addition, FDA policy requires that a physician be present).
- In order to approve research, the IRB must determine that all of the requirements specified in 45 CFR 46.111 (and if applicable, 21 CFR 56.111) are satisfied.
  See: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm and www.fda.gov/oc/ohrt/irbs/appendixc.html.
- A majority of the members present at the meeting must approve the research.
- IRB members who have a **conflict of interest** in a research project may provide information to the IRB, but cannot participate in the review. Members with a conflict do not count toward the quorum for that review.
- The IRB must notify investigators and the institution in writing of its decision to approve, modify or disapprove the research.
- IRBs must keep detailed documentation of meeting activities including attendance, voting on actions, the basis for the actions, and a written summary of the IRB discussion of controverted issues and their resolution.

Although not specifically addressed in the regulations, IRBs may employ a "primary reviewer system". In such a system, all IRB members receive basic information about the research application, but a "primary reviewer" with experience and/or expertise in the study area is assigned to conduct a thorough review of the IRB application and any accompanying documentation (e.g., an Investigator's Brochure or grant application). The "primary reviewer" will then report his/her findings for discussion at a convened meeting of the full board.

Reviewers may contact the investigator with questions or suggestions prior to the meeting. The IRB may ask that investigators attend the IRB meeting or be available by phone to answer questions that may arise at the meeting.

4.2 Expedited Review

Federal regulations permit the IRB chairperson or one or more experienced members to review a study if it involves no more than minimal risk for the subjects and if it fits within certain categories. The term "Expedited Review" only describes the process by which an IRB submission can be reviewed. The information the expedited reviewer(s) is required to consider is the same as if the submission were receiving Full Committee Review.

The Federal Regulations establish two main criteria for an expedited review. There are:

- The research may not involve more than "minimal risk".
    - "Minimal risk" means that “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” ([45 CFR 46.102(i)] and [21 CFR Part 56.102(i)])
- The entire research project **must be consistent** with one or more of the following federally defined categories (quoted from the OHRP, the IRB oversight agency, guidance document on Expedited Reviews.)

Some institutions/IRBs have additional requirements. Check with the IRB office for more information about how expedited review is handled by your IRB.

4.3 Research Categories that Qualify for Expedited Review

Federal Regulations establish 9 categories that IRBs may use to invoke the expedited review process. Institutions may adopt some or all of the categories when determining if a research activity can be appropriately reviewed by an expedited review process. Categories 1 through 7 pertain to both the initial and to the continuing IRB review. Categories 8 and 9 pertain only to continuing review. The 9 categories are listed below. Follow the hyperlinks for more details about each category. Hyperlinks will open in a new browser window. Close the new window to return here.

4.3.1 Category 1

Clinical studies on drugs or medical devices for which an investigational new drug (IND) or an investigational device exemption (IDE) application is NOT

required. Similarly, a study with a cleared/approved medical device that is being used in accordance with its cleared/approved labeling. More details

4.3.2 Category 2

Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture. More details

4.3.3 Category 3

Prospective collection of biological specimens for research purposes by noninvasive means. More details

4.3.4 Category 4

Collection of data through noninvasive procedures routinely employed in clinical practice provided that:

- The noninvasive procedure must not involve general anesthesia or sedation routinely employed in clinical practice or procedures involving x-rays or microwaves.
- Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples of noninvasive procedures are:
Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy

- Weighing or testing sensory acuity.
- Magnetic resonance imaging.
- Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography

Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual. More details

4.3.5 Category 5

Research involving data, documents, records, or specimens that:

- Have been collected.
  or
- Will be collected solely for non-research purposes (such as for medical treatment or diagnosis).

Note: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is ***not*** exempt. More details

4.3.6 Category 6

Collection of data from voice, video, digital, or image recordings made for research purposes. More details

4.3.7 Category 7

Research on individual or group characteristics or behavior. More details

4.3.8 Category 8

Continuing review of research previously approved by the convened IRB **where**:

- The research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; ***and*****,** the research remains active only for long-term follow-up of subjects,

  Or where:
- No subjects have been enrolled and no additional risks have been identified.

  Or where:
- The remaining research activities are limited to data analysis. More details

4.3.9 Category 9

Continuing review of research not conducted under an investigational new drug (IND) application or investigational device exemption (IDE) and where categories two (2) through eight (8) do not apply. More details

4.3.10 Expedited Review Process

The IRB chairperson or one or more experienced IRB members, designated by the Chair, can conduct an expedited review. IRB members with a conflict of interest can not be designated to serve as an expedited reviewer. In conducting the review, a determination must be made that the research meets the conditions for expedited review procedures.

The reviewer conducting the expedited review may exercise all of the authorities of the IRB with one important exception, the reviewer may not disapprove research. To approve a research activity, the reviewer must make the determination that all of the requirements specified in Federal regulations (45 CFR 46.111 and 21 CFR 56.111) are satisfied. The reviewer (s) may either approve the research, require modifications (to secure approval) or refer the research to a convened IRB meeting for review in accordance with the "full committee review" procedures described in section 2 above, and set forth in DHHS regulations at 45 CFR 46.108(b) and 21 CFR 56.108(c).

Expedited procedures can also be used to review minor modifications of previously approved research. [45 CFR 46.110(b) and 21 CFR 56.110(b)]

4.4 Review for Exemption Status

Federal regulations specifically define 6 categories of human subjects research that are ***exempt*** from the other provisions of the regulations. Federal Guidance indicates that applying exempt status to a project is a decision to be made by the IRB and that investigators can not make this determination for themselves. Therefore, institutions / IRBs have established procedures to certify that a project is exempt. Check with the IRB office to find out who has been granted authority to make the exemption determination. *Note: the determination must be made prior to initiation of research or of the activity; it cannot be made retroactively.*

4.5 Research that is Exempt

The following six categories of research are eligible for exemption status, [**45 CFR 46.101(b)**]: See the hyperlinked material for the regulatory details and conditions associated with each category. The links will open in a new browser window. Close the new browser window to return here.

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices. More Details

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior. Some Observations studies do not qualify

for exemption More Details,

3. Research not exempt under "2" above, may still qualify for an exemption if the human subjects are elected or appointed public officials or candidates for public office. More Details

4. Research involving the collection or study of freely available de-identified existing data, documents, records, pathological specimens, or diagnostic specimens. More Details

5. Research and demonstration projects conducted by heads of government departments or agencies which are designed to evaluate public programs. More Details

6. Taste and food quality evaluation and consumer acceptance studies. More Details

4.6 When Exempt Review is Not Appropriate

According to the DHHS regulations 45 CFR 46, NO research involving prisoners, as subjects, can be exempted.

4.7 Additional HIPAA Requirements that Indirectly Impact Exemption Review

The Privacy Rule is a Federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996. [45 CFR 160 and 164]. If an IRB has been given the responsibility to consider HIPAA in research issues and if the research potentially falls under the purview of HIPAA, an IRB will be applying not only the 45 CFR 46 exemption categories but also determining if HIPAA applies. In some cases, HIPAA applicability requirements are more stringent than DHHS exemption requirements and in other cases less stringent. A research project that is exempt from the human research subject IRB requirements may not be exempt from HIPAA provisions. Also, a project that is not exempt from IRB might be exempt from HIPAA. See the DHHS OHRP "Guidance on Research involving Coded Private Information or Biological Specimens," and the NIH and guidance entitled "Institutional Review Boards and HIPAA Privacy rule".

5 Process of Working with the IRB

5.1 Criteria for IRB Approval

Federal policy lists **Basic Criteria** that the IRB must apply [45 CFR Part 46.111 and 21 CFR Part 56.111] when reviewing research involving human subjects. To approve a research project, the IRB must determine that:

- The risks to subjects are minimized.
- The risks are reasonable in relation to any anticipated benefits to the subject, and to the advancement of knowledge.
- The selection of subjects is equitable.
- Informed consent will be sought.
- Informed consent will be documented.
- Where appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure safety of subjects.
- There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- Where any of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect subjects.

In addition, there are specific requirements regarding the informed consent process. These will be detailed in Module 3, "Informed Consent".

The IRB must determine that these conditions exist at the time of initial review and at each subsequent review conducted by the IRB

5.2 Types of IRB Submissions

1. **Application for initial review:** The first request for approval of a specific project is the application for initial review.
2. **Application for continuation review:** The IRB must re-review studies at a minimum of once every 365 days. An IRB may require review more frequently depending on the IRB's assessment of the study's risk/benefit ratio. The review may be a full or expedited review.
3. **Amendments or modifications:** Changes can not be made to approved studies, including the informed consent document, without prior IRB review and approval. The review may be full or expedited, depending on the magnitude of the change and the effect of the change on the risks / benefit ratio.
4. **Reports:** The IRB may require a report for:
    a. Adverse events or unanticipated problems involving risks to subjects or others.

b. Incidences of noncompliance.
c. Deviations from an approved study protocol and violations of the terms of approval.
d. Data Safety and Monitoring Report summaries.

5.2.1 Application for Initial Review

The initial review may be either a "Full Committee" or "Expedited" review.

5.2.2 Application for Continuation Review

The IRB must do substantive continuing review and must consider the same issues as during initial review. Specifically:

- When conducting a continuation review, the IRB uses "Full Committee Review" procedures unless the research meets the expedited review criteria.
- To approve research, the IRB must determine that all the requirements for initial approval (specified in 45 CFR 46.111 and 21 CFR 56.111) continue to be satisfied.
- IRB should review, at a minimum, the protocol and any amendments as well as a status report including:
  - The number of subjects accrued.
  - A description of adverse events, unanticipated problems, withdrawal of subjects, complaints, summary of relevant new information.
  - A copy of current informed consent document.

Follow the link to view the latest GUIDANCE FROM OHRP ON IRB CONTINUATION REVIEW.

It is an investigator's responsibility to know when IRB approval will expire. However, most institutions/IRBs, as a courtesy to their investigators, send out reminders that IRB approval is about to expire. Sometime during the first year of IRB approval, investigators will receive a request to complete a progress report for continuing review by the IRB. It is an investigator's responsibility to complete the continuing review request, submit it back to the IRB in a timely manner prior to the end of the current IRB approval period.

If a protocol's approval expires before the IRB completes its Continuation Review, the investigator should stop all procedures that are not needed to ensure the health and safety of the research subjects.

5.2.3 Amendments and Modifications

All amendments and modifications to a study need IRB approval before they are implemented. If the investigator wants to change *anything* in the research that would impact the subjects, such as recruitment procedures, key personnel, inclusion/exclusion criteria, research procedures, the informed consent document / process, or data elements collected, the investigator must obtain IRB review and approval prior to implementation of the changes. The only exception are changes necessary to immediately protect subjects' safety, as noted in 21 CFR 56.108(a)(4) and 56.115(a)(1). If an investigator is unsure about reporting changes to the IRB, he/she should call the IRB office and ask for guidance. The IRB office can also provide investigators instructions for submitting a request to modify an IRB approved research

5.2.4 Reports of Unanticipated Problems / Adverse Events / Noncompliance to the IRB

Federal reporting requirements for IRBs, investigators, and funding sponsors are confusing and contradictory. Consequently, IRBs tend to develop their own idiosyncratic reporting requirements, based upon their interpretation of both FDA and OHRP guidance. This poses some difficulty for investigators because if the project is funded, the sponsor may have reporting requirements that differ from the IRB policy and procedures.

At a minimum, to ensure compliance, the investigator is responsible for:

1. Determining the IRB requirements for reporting with respect to what needs to be reported, when it should be reported, and the procedure for submitting the report.

2. Setting up systems to ensure that reportable events are identified and submitted to the IRB in a timely manner.

Examples of the type of events that may be reportable include:

- An unanticipated problem which may be defined as any unexpected event that affects rights, safety or welfare of subjects. The event could be physical such as an adverse drug experience or adverse device effect. The event could also involve some harm or risk (i.e. breach in confidentiality or harm to a subject’s reputation).

- Serious adverse event which may be defined as a death, life-threatening adverse drug or device experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent disability/incapacity, or a cognitive anomaly/birth defect.

- Protocol exceptions which may be defined as enrollment of a research subject that fails to meet protocol inclusion/exclusion criteria.

- Protocol deviation which may be defined as a departure from the protocol as approved by the IRB for a single subject.

- Data and Safety Monitoring Plan or Board summary reports.

- Complaints concerning subject rights submitted by subjects or concerned parties, family members, or study personnel.

The IRB will use the reports to assess whether the risks/benefit ratio is still reasonable, whether changes in the informed consent document or study procedures are needed, or whether re-consent is necessary. IRB requirements for reporting vary regarding what should be reported, when the reports should be submitted, and the format of the reports. Check with your IRB to determine its specific requirements.

5.3 Additional Reporting Requirements

Besides the IRB, the Principal Investigator (PI) has a variety of entities to which he/she is responsible for reporting. Minimum reporting requirements for each entity are:

Entity	PI Reporting Requirements
Research Subject	While it might not be considered reporting in the strictest sense, the *informed consent process* is a report to the potential subject about the research, both before the research begins and on an ongoing basis throughout the study. Also, if new information becomes available during the research that might impact the subject's willingness to participate, an investigator is obligated to provide the subject with that information. This information will also need to be reported to the IRB. The IRB office can provide guidance on how additional information should be reported.
Institution	Most institutions have reporting lines set up so that the investigator makes reports to the IRB and it falls upon the IRB to keep the institution informed. However, check with the local IRB to make sure that the investigator does not have direct responsibility for reporting incidents to the institution.
Sponsor	Adverse events should be reported immediately to the sponsor. Investigators should also check with the sponsor about proposed changes that might be made to the study, based on the adverse event that has occurred or preliminary findings. The sponsor also should be told about serious or ongoing noncompliance in a study.
FDA	Adverse events should be reported directly to FDA if the research is PI-

	initiated (without external sponsorship) and falls under the FDA's purview.
DSMB	If your project has a Data Safety and Monitoring Board, check your DSMB plan for reporting requirements.

5.4 Record Keeping

The signed informed consent document is one of the most critical research records the investigator needs to obtain and keep. It provides verification that the research was explained to the subject and that the subject understood and voluntarily agreed to participate in the research study. Investigators are responsible for retaining signed consent documents, IRB correspondences, and research records for at least 3 years after the completion of the research activity. However, local institutional policy or sponsoring agency requirements may dictate that records be kept longer. Check with the sponsor and IRB office to make sure that the minimum 3 years retention requirement meets their needs.

The FDA regulations specify unique document retention requirements for FDA regulated studies [see 21 CFR Part 312.62 (c)]. These requirements must be met for FDA regulated studies.

6 Other Regulations and Regulatory Groups

6.1 Funding and Regulatory Agencies

Depending upon the nature of your research and the agency that funds your research there are a number of other regulations, policies and procedures that may need to be considered. Below is a brief description of selected regulations, regulatory bodies, and funding agencies that may oversee your research. Funding agencies and /or your local IRB offices can also provide guidance on whether any additional requirements apply to a research activity. Hyperlinks will open in a new browser window. Close the new browser window to return here.

Funding Agency / Regulatory Agencies	General Regulations
DHHS The Department of Health and Human Services (DHHS) is responsible for one group of human	The DHHS 45 Code of Federal Regulations (CFR) Part 46 applies to all human research submitted to or funded by Department of Health and Human Services and is applied to all human research by most large institutions. Subparts include: **Subpart A:** Basic Federal Policy for the Protection of Human Subjects

subjects federal regulations.	**Subpart B:** Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research **Subpart C:** Additional Protections for Prisoners **Subpart D:** Additional Protections for Children
NIH The National Institutes of Health include funding agencies that provide federal funding for biomedical research. NIH requires grantees conducting certain types of clinical research studies to have either data safety monitoring plans and/or data safety and monitoring boards. In general NIH policy requires that a Data and Safety Monitoring Board be established for all phase III randomized clinical trials.	(1) NIH Policy for Data and Safety Monitoring. (2) Policy for the National Cancer Institute for Data and Safety Monitoring of Clinical Trials. (3) Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute. (4) Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials.
OHRP The Office for Human Research Protections is the DHHS oversight body that provides guidance to IRBs and investigators conducting human subject research.	OHRP Policy and Assurances guidelines, regulations, ethical principles, IRB Guide Book, OHRP/OPRR Reports, FAQs, and other materials relevant to the protection of human research subjects are available from the Office for Human Research Protections Website.
FDA The Food and Drug Administration	The Food and Drug Administration (FDA) has numerous regulations directly impacting informed consent. See Guidance documents, information sheets and regulations indirectly impacting IRBs and investigators.

oversees the use of all drugs, devices, biologics, etc. including their use in research with human subjects.	
ICH/GCP. International Conference on Harmonization / Good Clinical Practices.	Human subject research that is conducted in international settings may have additional requirements that must be met such as, International Conference on Harmonization / Good Clinical Practices
Department of Education.	Research that is funded by the Federal Department of Education may have additional requirements that must be met.
Department of Veterans Affairs.	Research involving human subjects recruited from or conducted in a Veterans Affairs facility must also meet the requirements as set forth in the VA Manual 1200.5
Other Federal Agencies.	Each federal agency may have additional policies, procedures, requirements, etc. that must be applied to research involving human subjects. Examples are the Department of Defense, Department of Energy, and National Science Foundation .

6.2 Assurance Requirements

If DHHS regulations apply to research being conducted at an institution, the institution must have an "Assurance" on file with the DHHS Office for Human Research Protections (OHRP). The Assurance outlines the institution's responsibilities for meeting the requirements for 45 CFR 46.103 and documents how the institution will protect the welfare and rights of research subjects based on federal regulations. The Assurance encompasses:

- A statement of principles.
- Designation of IRBs.
- A list of members on the IRB.
- Written operating procedures for the human subject protection program.
- Training in human subject protections.

Everyone on the research team has a responsibility to understand the institution's written policies and procedures.

6.2.1 Contact the IRB office to:

- Ensure the organization is registered with OHRP if federal dollars are funding the research.
- Obtain the Federal Wide Assurance (FWA) or Multiple Project Assurance (MPA) number. Alternatively, this information can be found on the OHRP Website.
- Determine FWA requirements for multi-sites research activities.

Genetic Research in Human Populations

1 Introduction

Genetics research raises ethical issues that differ in many ways from those that arise in other kinds of human subjects research. Some of these differences are of kind and some are of magnitude. We can locate the leading ethical issues under the following headings:

- **Privacy and confidentiality.**
- **Informed consent.**
- **Risks of harm.**

2 Privacy and confidentiality

The terms "privacy" and "confidentiality" are not synonymous. Generally, "privacy" refers to *persons* and "confidentiality" to *information*. If, for instance, one surreptitiously obtains a quantity of residual blood from hospital testing and analyzes it for cancer markers or mutations, then we should say that the blood source's privacy has been violated. If, on the other hand, one were to sneak a look at the source's medical record and learn that she has breast cancer, her confidentiality has been breached.

For a number of reasons, including increased risk of bias, discrimination and stigma, genetic privacy and confidentiality are sometimes thought to be more important than privacy and confidentiality in other kinds of research. Genetic information is for these reasons sometimes likened to information about sexually transmitted diseases or certain mental health problems.

Investigators preparing to conduct genetic analyses must tell potential subjects which entities and persons will have access to the data. This might include investigators at other institutions, corporate sponsors, a government, employers, insurance companies, etc. If information obtained during research will be placed in a patient's medical record, this too must be disclosed. Subjects must also be told of the risks of an employer or insurer having access to an individual's genetic information.

Unlike most other kinds of health data, genetic information applies to or is about more than one person. Analyze genomes and you will learn something about a person's parents, siblings, children, and perhaps others. This means that individuals can lose privacy and/or confidentiality even if they are not the source of the specimen or information being studied.

For instance, confirming a genetic diagnosis of Huntington's disease in a person also means that at least one of his or her parents carries this gene and is at risk of developing the condition. But the parent is not a subject in the research and did not consent to it.

Research that includes follow-up studies and attempts to identify clinical correlations requires that a subject's unique information be linked to the genetic information. These links, in conjunction with particular aspects of research protocols, might be used to seek out or re-contact subjects in the future. These links and their uses must be disclosed to subjects.

For this and other reasons, many investigators seek to unlink or decouple personal identifiers from genetic data or biological specimens. Successful unlinking reduces or eliminates some threats to privacy and confidentiality. However, it is increasingly possible to take even "unlinked" data or samples and use "surrogate identifier ensembles" (demographic information, birth date, postal code, diagnostic code, etc.) to pick out or identify a unique individual. Some scholars question whether genetic samples can ever be completely unlinked or "anonymized."

3 Valid Consent

Ethical research on humans generally requires that three conditions be met. Subjects must be:

- Adequately informed.
- Free from coercion or undue influence.
- Competent.

3.1 Adequate Information

Many familiar challenges in human subjects are based on questions or difficulties that arise in meeting these three conditions. In the case of genetics research, the challenges are amplified. For instance:

- It is difficult in the case of traditional medical and behavioral research to determine how much information is adequate and, moreover, what level of complexity or detail is appropriate. These problems are magnified by genetics research, which most non-scientists find difficult to understand.
- It is often unclear how to describe risks of harm to potential subjects. In genetics research, the risks are generally not physical but psychological,

social, economic, etc. These risks are sometimes more difficult to present and evaluate.

- In pedigree and other studies, information collected might affect entire families, including members who do not wish to know or participate. Special precautions are needed to protect against or manage pressure or coercion and to communicate risk. There is growing urgency to include genetic counseling in the consent process for genetics research.

3.2 Autonomous Consent

The consent process must take into account the questions whether and when investigators will re-contact subjects. If the samples will be unlinked and researchers will not inform subjects of any results, this must be disclosed. If subjects want the results they can then be urged to be tested independent of the research. If re-contact is possible but not planned, disclosure is required for the same reason. If re-contact is planned—perhaps to measure subsequent clinical correlations—disclosure is crucial for those who might not want to know their genetic status.

Generally speaking, the following are some items that should be disclosed to prospective subjects during the consent process:

- The purpose of the research, in simple language.
- How the specimens will be stored and who will have access to them or the information they contain.
- Whether sources will be re-contacted later with information about the study findings.
- Whether the samples are linked to the sources with a code or identifier. (If a sample is coded it is linked and therefore not anonymous.
- Whether the research will be used to develop proprietary products or assays and whether the subject can share any financial rewards from the project.

4 Risks of Harm

One of the most difficult components of the consent process in genetic research is how to identify and communicate risks of harm. The harms that might result range from minor to major, and from physiological to psychosocial and even economic.

- Blood draws carry a risk of bruising.

- The idea of testing can cause pre- and post-test anxiety, which can vary with existence/availability of treatment.

- Disclosure of results may result in employment and social bias, discrimination and stigmatization.

- Disclosure of results may cause loss or increased cost of health and/or life insurance.

- Family members of the index subject may face similar risks of harm.

It can be very difficult to assess these risks. "Anxiety" will vary by individual and malady, and the most frequently cited risks of genetic research (loss of insurance or health benefits and employment discrimination) are dependent on the existence of legislation to prevent such discrimination. This varies by jurisdiction.

Further, "stigmatization" can be quite vague, perhaps even subjective. Yet there is growing evidence of some ethnic groups and subgroups becoming associated with genetic disorders. This possibility should be disclosed to potential subjects.

Note that the concept of "risk" includes the notion of probability or likelihood. In other words, risks are inherently probabilistic. For this reason, the phrase "potential risk" is redundant. The risks are quite real—they just might not be realized. Some think the phrase "potential risk" therefore misleadingly downplays the chances that a subject will come to grief.

5 Stored Biological Samples

Research on stored biological samples allows investigators to conduct studies long after the subject has moved on. It is helpful to think of research on stored samples as two kinds:

- Retrospective, in which investigators use blood, tissue, etc. from pre-existing collections.

- Prospective, in which investigators collect samples to create new banks.

5.1 Retrospective Research

If the research is retrospective and if adequate steps are taken to prevent identification of the samples' sources, then genetic research can often proceed without an IRB requiring that individual subjects provide valid consent. The benefits of such research can be quite valuable and may outweigh the violation of the principle of obtaining informed consent from all the sources of stored

biological samples. However, an IRB must scrutinize such waivers of consent carefully.

Even if federal regulations may permit research on existing samples without consent, an IRB may determine that consent is necessary if the cohort is small, the disorder or trait is stigmatizing, and there are concerns about maintaining confidentiality. Note that if it is possible to re-contact sources, the following problem needs to be addressed.

Suppose you have received IRB approval to study banked tissue without obtaining the consent of the tissue sources. Your protocol meets the federal criteria for waiver of consent. Now imagine that you discover a medically important mutation in the tissue sample belonging to patient XYZ. You do not know who XYZ is, or even if s/he is alive. But you can find out XYZ's identity because the sample is linked to patient records with a code number. *Should you use the link to find and warn XYZ? What if XYZ does not want to know of this malady, and you tell her anyway? What if she would want to know, and you don't tell her? What about XYZ's children? Is there a duty to warn or inform them?* Laws and regulations do not usually address these difficult ethical issues. On the other hand, consent is required to take blood or tissue for prospective genetic studies.

5.2 Prospective Research

IRBs face difficult challenges when investigators seek permission to bank or archive biological specimens for future, unspecified, research. If investigators want to bank tissue but are unable to say what it will be used for, then it is difficult to obtain valid consent at the time of recruitment, at least if one assumes that subjects must know the purpose of the research to consent to it.

It is possible to inform prospective sources/subjects that their tissue will be banked for future, unspecified research, but this is increasingly difficult. *Will the samples be used for research in cancer genetics or behavioral genetics? Will results be correlated by race or ethnicity? Will the results be used to develop proprietary products?* These are all questions that subjects increasingly want answered before they consent to participate in research.

Indeed, the secondary use of tissues or the information they contain is emerging as one of the greatest challenges of genetic research. Researchers need to consider how much information is adequate at the outset to permit subsequent analysis to be conducted without additional consent.

The growth of bioinformatics, or computational genomics, makes it clear that in the near future the concern will not be so much with stored biological samples but with digitized samples—electronic data that can be stored, transmitted, and analyzed with new ease and power.

HISTORY AND ETHICAL PRINCIPLES 2

History and Ethical Principles

1 Introduction

The first century physician Celsus justified experiments on condemned criminals in Egypt using wording that became a classic defense for hazardous experimentation: "It is not cruel to inflict on a few criminals sufferings which may benefit multitudes of innocent people through all centuries." [Brady and Jonsen]. Both the ethics and regulation of human subjects research have changed considerably since Celsius' time. This module discusses the evolution of the ethical principles, and how they have influenced research involving human subjects.

By the end of this module you will be able to:

- **Discuss why ethics is important when conducting research involving human subjects.**
- **Describe the major historical events that have influenced how research involving human subjects is conducted today.**
- **Identify problems with studies that have violated ethical standards.**
- **Describe the Belmont Principles.**
- **Discuss the role that IRB review plays in ensuring the ethical design and conduct of research.**
- **Discuss the role that the regulations play in preserving the public trust.**

2 Why Ethics is Important

We are concerned here with normative ethics that tell us how things ought to be, not what is. These are the rules that we use to make decisions and to assess or justify actions and behavior. In research, these rules answer the questions: How should researchers behave? How should researchers not behave? How should we determine what research should be conducted? How should we determine what research should not be conducted?

There are many advantages to understanding research ethics. Ethical principles:

- Provide us with a structure for analysis and decision-making.
- Support and remind researchers to protect human subjects.

Historical Development

The events that led up to the development of current thinking on human research protections and the regulatory system now in place occurred in both biomedical and social/behavioral research.

3 Events in Biomedical Research

3.1 Nuremberg Code

At the end of World War II, 23 Nazi doctors and scientists were put on trial for the murder of concentration camp inmates who were used as research subjects. It became clear during the trial that no accepted standards existed regarding the conduct of human research. The court found that it could not convict the defendants of violating the rights of research subjects. However, the court did convict 15 of the 23 defendants of murder. The court condemned 7 to death by hanging, sentenced 8 to prison from 10 years to life, and acquitted 8. [Mitscherlich & Mielke] To fill the void in the absence of a legal standard for research the court included in the legal judgment ten points describing required elements for conducting research with humans. These points became known as the Nuremberg Code.

In summary, the Nuremberg Code includes the following guidance for researchers:

- Informed consent is essential.
- Research should be based on prior animal work.
- The risks should be justified by the anticipated benefits.
- Only qualified scientists must conduct research.
- Physical and mental suffering must be avoided.
- Research in which death or disabling injury is expected should not be conducted.

3.2 Effect of the Nuremberg Code

The Code had little impact on researchers in the United States, who thought that the principles in the Code were already implicit in their work and that it was simply a document to condemn the Nazi atrocities and to convict the Nazi doctors. There were a number of problems with the Code itself. For example it did not have the strength of law, it was created after the conviction of the Nazi doctors, and it applied to only non-therapeutic human subjects research.

3.3 Declaration of Helsinki

In 1964 the World Medical Association developed a code of research ethics that came to be known as the Declaration of Helsinki. It was a reinterpretation of the Nuremberg Code, with an eye to medical research with therapeutic intent. Subsequently, journal editors required that research be performed in accordance with the Declaration. In principle, this document set the stage for the implementation of the Institutional Review Board (IRB) process. [Shamoo & Irving]

3.4 Beecher Article

In 1966 Dr. Henry K. Beecher, an anesthesiologist, wrote an article (Beecher HK. "Ethics and Clinical Research" NEJM June 16, 1966) describing 22 examples of research studies with controversial ethics that had been conducted by reputable researchers and published in major journals. Beecher wrote, "medicine is sound, and most progress is soundly attained;" However, if unethical research is not prohibited it will "do great harm to medicine." Beecher provides estimates of the number of unethical studies and concludes, " unethical or questionably ethical procedures are not uncommon." [Beecher] Beecher's article played an important role in heightening the awareness of researchers, the public, and the press to the problem of unethical human subjects research. *"Until this article we assumed that unethical research could only occur in a depraved regime like the Nazis."*- Robert J. Levine, MD (personal communication).

3.5 The Public Health Service Syphilis Study (1932-1971)

One of the seminal events in the development of the current regulatory environment was the Public Health Service (PHS) Syphilis Study (1932 – 1972), the so-called "Tuskeegee Syphilis Study" [see "Bad Blood: The Tuskegee Syphilis Experiment", Revised Edition by James H. Jones] . Initiated and funded by the PHS, this study was designed initially to make treatment available to African-American men with syphilis, although at the time the study began there was no known effective treatment. After funding to make drugs available was cut, the study became a natural history study. Hundreds of men with syphilis and hundreds of men without syphilis (serving as controls) were enrolled into the study. The men were recruited without their informed consent. They were deliberately misinformed about the need for some of the procedures. For example, spinal taps were described as necessary and special "free treatment."

Even after penicillin was found to be a safe and effective treatment for syphilis in the 1940's, the men were denied antibiotics. To prevent them from being treated by the military or by local physicians, the investigators arranged with the local draft board to prevent the men from being drafted, arranged with local physicians to withhold treatment, and told the men that if they volunteered for the military, they would no longer receive financial compensation for taking part in the study.

The study continued to track these men until 1972 when the first public accounts of the study appeared in the national press. The study resulted in 28 deaths, 100 cases of disability, and 19 cases of congenital syphilis. [Levine]

Ethical problems: lack of informed consent, deception, withholding information, withholding available treatment, putting men and their families at risk, exploitation of a vulnerable group of subjects who would not benefit from participation.

3.6 Recent Events

In the last several years reports of unethical studies including gene transfer, cancer, and psychiatric research have heightened the public awareness of these issues even further. Two recent examples follow:

3.6.1 Death of a Normal Volunteer

On March 31, 1996, a 19-year-old Asian -American student at the University of Rochester responded to an advertisement for study subjects to undergo bronchoscopy for the harvest of alveolar macrophages. The bronchoscopy was difficult and required numerous doses of topical lidocaine. The investigators repeatedly asked the subject if she wanted to continue and the subject nodded her head "yes." The study was completed, but the subject returned to the hospital in cardiac arrest from an overdose of lidocaine and died April 2, 1996. An investigation into this death revealed that the protocol did not limit lidocaine doses, that the doses were not documented, that the subject was not observed after the bronchoscopy, and that the concentrations of lidocaine were increased without IRB approval.

3.6.2 Death on Gene Therapy Trial

In the fall of 1999, eighteen-year-old Jesse Gelsinger died as a result of his participation in a gene transfer trial. Jesse had a rare metabolic disorder, ornithine transcarbamylase deficiency syndrome (OTC) that was being controlled by medication and diet. Researchers were testing an innovative technique using adenovirus gene transfer. Shortly after treatment Jesse Gelsinger experienced multiple organ failure and subsequently died. This case catapulted research with human subjects into the national media. Serious concerns related to conflict of interest, data safety monitoring, and informed consent have made the Gelsinger case a contemporary illustration of continued doubts about the ethical integrity of research with human subjects. This case has instigated deliberations on all these controversial topics at the national level. The outcome of the discussions has yet to be determined.

4 Events in Social & Behavioral Research

4.1 Wichita Jury Case (1953)

In this study researchers tape recorded jurors' deliberations in six courtroom trials to measure the influence of attorney comments on decision making. The judge and attorneys knew the research was being conducted, but the jurors did not. The tapes were played at a law conference. The resulting concern that future taping could have a repressive effect on juror deliberations resulted in federal law banning all recoding of jury proceedings in 1956.

Ethical problems: compromising the integrity of important social institutions, lack of informed consent, invasion of privacy.

4.2 Milgram "Obedience to Authority Study" (1963)

The purpose of this study was to learn more about how humans respond to instructions from people in positions of authority. The researchers informed volunteers that the purpose of the research was to study learning and memory. Each subject was told to teach a "student" and to punish the students' errors by administering increasing levels of electric shock. The "students" were confederates of the researcher and were never actually harmed. The "students" pretended to be poor learners. They mimicked pain and even unconsciousness as the subjects increased the levels of electric shock. Sixty-three percent of the subjects administered what they thought were lethal shocks; some even after the "student" claimed to have heart disease. Some of the subjects, after being "debriefed" from the study experienced serious emotional crises.

Ethical Problems: deception, unanticipated psychological harms.

4.3 Humphrey "Tea Room Trade Study" (1970)

The study planned first to obtain information about homosexual practices in public restrooms and then to conduct further investigation on the men who took part in the acts. The researcher went undercover and gained the confidence of the men by acting as a "look out." The researcher identified 100 active subjects by tracing their car license numbers. A year after he completed the initial study of direct observation of homosexual acts the researcher distributed a "social health survey" throughout the communities where he knew the subjects lived and collected data about their sexual orientation, and marital and family status.

Ethical problems: invasion of privacy, use of a vulnerable population, lack of informed consent. [Warwick]

4.4 Zimbardo "Simulated Prison" (1973)

This landmark psychological study of the human response to captivity and, in particular, prison life, involved assigning roles to male student volunteers as "prisoners" and "guards". The research became so intense, as physical and psychological abuse of "prisoners" by "guards" escalated, that several of the subjects experienced distress less than 36 hours after the study began. Dr. Philip Zimbardo, the researcher, failed to stop the experiment/simulation until six days had passed. See Dr. Zimbardo's web site for more details on this study.

Ethical problems: harm to subjects, neutrality of researcher.

4.5 Restaurant Letter Study (2001)

Not all the events that raise concerns about research ethics occurred in the past. Recently, a faculty member from the Business School of a major university designed and implemented a study to elicit responses from restaurants to complaints from putative customers. As part of the project, the researcher sent letters to restaurants falsely claiming that he and/or his wife had suffered food poisoning that ruined their anniversary celebration. The letters disclaimed any intention of contacting regulatory agencies and stated that the only intent was to convey to the owner what had occurred "in anticipation that you will respond accordingly." Restaurant owners and employees suffered severe emotional distress before learning that it was a hoax. The researcher later admitted the falsehood in a letter of apology. He explained that "the letter was fabricated to help collect data for a research study that I designed concerning vendor response to customer complaints." This study had not been submitted to an IRB for review. An investigation by the Federal Office for Human Research Protections (OHRP) followed. In addition, the restaurants filed a lawsuit against the University.

Ethical problems: Deception, lack of informed consent, infliction of emotional distress.

5 Development of the Regulatory Process

In the aftermath of the events through the 1970s, the US Congress held hearings on "Quality of Health Care - Human Experimentation" in 1973. The hearings led to the National Research Act of 1974 which:

- Established the "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research"
- Required the establishment of IRBs at institutions receiving US Department of Health, Education and Welfare (now the Department of Health and Human Services) support for human subjects research

5.1 The National Commission

The charge of the National Commission was to:

- Identify the basic ethical principles that underlie the conduct of human research.

- Develop guidelines to ensure that human research is conducted in accordance with those principles, which, in turn, led to the current federal regulations.

5.2 Current Regulations

In 1974 the Department of Health, Education and Welfare issued 45 CFR 46 "Regulations for the Protection of Human Subjects of Biomedical and Behavioral Research". Based on the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978), the Department of Health and Human Services (HHS) revised and expanded its regulations for the protection of human subjects 45 CFR 46 in the late 1970's and early 1980's. In 1991 sixteen other federal agencies and departments agreed to apply the basic requirement in 45 CFR 46 to the research they fund or conduct, and in 2005, the Department of Homeland Security adopted the regulations. The basic regulations are referred to as the "Common Rule."

6 Ethical Principles

6.1 The Belmont Report

In 1979, after a several years of deliberations, the National Commission published the Belmont Report. The Report is a summary of the basic ethical principles identified by the National Commission in the course of its deliberations in February 1976 supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of the basic ethical principles and guidelines that should be used to resolve the ethical problems that surround the conduct of research with human subjects.

The Belmont Report identifies three basic ethical principles that underlie all human subject research. These principles are commonly called the Belmont Principles. The Belmont Principles are respect for persons, beneficence, and justice.

All individuals involved in the conduct of human research should read the **Belmont Report**. The conduct of ethical research is not intuitive – being a good person is no more sufficient for the conduct of ethical research than being brilliant is sufficient for the conduct of good science. One must know and understand the basic principles science and know how to apply them to the design and conduct

of research in order to do good science. So, too, must one know and understand the basic ethical principles in the Belmont Report and know how to apply them in order to conduct ethical research.

6.1.1 Respect for Persons

This principle is found in the writings of philosopher Immanuel Kant. It requires us to treat individuals as autonomous human beings and not to use people as a means to an end. We must allow people to choose for themselves and provide extra protection to those with limited autonomy.

Elements of autonomy include:

- Mental capacity, the ability to understand and process information.
- Voluntariness, freedom from the control or influence of others.

Therefore, subjects have full autonomy when they have the capacity to understand and process information, and the freedom to volunteer for research without coercion or undue influence from others.

Rules derived from the principle of respect for persons include:

- The requirement to obtain informed consent.

- The requirement to respect the privacy of research subjects.

6.1.2 Beneficence

This principle reminds us to minimize harms and maximize benefits. Derived rules include:

- The requirement to use the best possible research design to maximize benefits and minimize harms.
- The requirements to make sure the researchers are able to perform the procedures and handle the risks.
- The prohibition of research that is without a favorable risk-benefit ratio.

6.1.3 Justice

The principle of justice requires us to treat people fairly and to design research so that its burdens and benefits are shared equitably. Derived rules include:

- The requirement to select subjects equitably.

- The requirement to avoid exploitation of vulnerable populations or populations of convenience.

6.1.4 Balancing the Three Principles

It was the Commission's intention that each of the three principles should have equal moral force. This means that in some situations, the three principles might be in conflict with one another. For example, we might derive from the principle of respect for persons that we should limit the involvement of children in research because children are unable to choose for themselves. But, we might derive from the principle of justice that we must involve children in studies so that children will have the opportunity to benefit from the research. The *Belmont Report* says that one principle does not always outweigh another. Rather, we are required to consider each case separately and on its own merits in light of all three principles.

6.1.5 Applying the Belmont Principles

The need for protecting human subjects through research ethics and regulations is as relevant now as ever. Applying the Belmont principles to our studies is an important start:

- From the principle of respect for persons we need to conduct initial and continuing informed consent. We need to evaluate whether the research allows subjects to withdraw from the research and maintains the welfare of each subject.

- From the principle of beneficence we need to evaluate the social and scientific value of the research, the scientific validity of the research, and determine whether the research has a favorable risk benefit ratio.

- From the principle of justice we need to evaluate whether there is fair subject selection. We also need to evaluate the inclusion and exclusion criteria and the methods of recruitment.

6.2 Review by an Institutional Review Board (IRB)

In addition to providing ethical guidance for the conduct of research involving human subjects, the Belmont Principles form the basis for many of the requirements found in the federal regulations. In fact, the specific criteria for IRB approval spelled out in 45 CFR 46.111 of the regulations are drawn directly from the three basic Belmont Principles. Therefore, the Belmont Principles also serve as a guide to compliance with the federal regulations.

According to Section 111, in order to approve research the IRB must determine that all of the criteria in the section are satisfied. The following summarizes the criteria, along with the relevant principles from the Belmont Report:

- Risks to subjects are minimized [Beneficence]
- Risks are reasonable in relation to anticipated benefits [Beneficence] .
- Selection of subjects is equitable [Justice] .
- Informed consent is sought from each subject [Respect for Persons] .
- Informed consent is appropriately documented [Respect for Persons] .

And when appropriate:

- Data collection is monitored to ensure subject safety [Beneficence] .
- Privacy and confidentiality of subjects is protected [Respect for Persons & Beneficence] .
- Additional safeguards are included for vulnerable populations [Respect for Persons] .

The ethical principles and federal regulation provide a framework for IRBs to evaluate research involving human subjects. However, each research study is unique and a comprehensive review may be a complicated process.

6.3 Other Ethical Guidelines

Professional associations of social and behavioral sciences have adopted ethical guidelines for the conduct of human subjects research, including the American Psychological Association, the American Sociological Association, the American Anthropological Association, the Oral History Association, and others. These guidelines provide discipline-specific ethical guidelines, which help inform IRBs and researchers.

7 The Need for Independent, Objective Review of Research

Since the Belmont Report and the other professional ethics codes provide guidance on the ethical conduct of research, the question arises as to why we need IRB review. Why not just obtain a commitment from the researchers that they will follow the ethical principles in the conduct of their research? The answer is found in some basic principles of human nature.

7.1 Goals of Researchers

First, highly motivated people tend to focus on their goals and may unintentionally overlook other implications or aspects of their work. Take, for example, driving on the highway. When one is late for an appointment, one tends to drive faster and may be tempted to break the speed limit. It is not that the person does not care about safety; rather, at that moment they are focusing on the goal of getting to their appointment and not considering the safety implications of what they are doing. What keeps most people from driving at excessive speeds is that there is a system in place that results in consequences for people who drive at unsafe speeds. Researchers are highly motivated people who tend to focus on their scientific goals, just as drivers focus on getting to an appointment on time. As a result, they may overlook the ethical implications of what they are doing. The purpose of IRB review is to provide a system that requires researchers to take ethics into account when designing and conducting their research or there will be consequences.

7.2 Objectivity

The second principle of human nature that drives the need for IRB review is that no one can be totally objective about his or her own work. One way that this affects the conduct of research is that people underestimate the risks resulting from projects with which they are very familiar. For example, cars had seat belts for years, but people rarely wore them until there were laws requiring seat belt use. Most people understood that seat belts saved lives and prevented injury, so why didn't they use them? In part, people underestimated the risk of having an accident while driving because they drove on a daily basis. Similarly, researchers tend to underestimate the risks of their research, not because they are callous, but because the procedures are so familiar to them. In addition to underestimating risks, researchers have an inherent conflict of interest when judging their own research. They have a stake in getting the research done as quickly and efficiently as possible. As a result of both of these principles, every research activity needs an independent, objective review. This is one important function of the IRB review process.

Even if researchers were well versed in the ethical principles and committed to the ethical conduct of research, IRB review is necessary to ensure that ethical concerns are not overlooked.

8 Public Trust

In addition to ethical principles, the regulations also reflect the need to maintain the public trust in research. Researchers do not have the right to conduct research, especially research involving human subjects. Society grants researchers the privilege of conducting research. The granting of that privilege is

based on the public's trust that research will be conducted responsibly. Erosion of that trust can result in the withdrawal of this privilege.

The federal regulations that currently govern human subjects research evolved as a response to the erosion of public trust that resulted from the scandals described above. Without regulations, these events caused the public to question the ethics of researchers conducting human subjects research. Congress, responding to public concern, directed that federal agencies to adopt regulations for research funded or conducted with federal funds and for research using products regulated by the U.S. Food and Drug Administration (FDA). Should additional events erode the public trust, Congress will order additional restrictions and could even ban some types of research altogether.

Public trust is maintained through accountability – the ability of researchers to demonstrate to others that they are conducting research responsibly. Accountability is accomplished through documentation. It is not sufficient for researchers to conduct ethical research. They need to be able to document that they have done so. Therefore, in addition to setting standards for the ethical conduct of research involving human subjects, the federal regulations include requirements for the necessary documentation of that ethical conduct. The purpose of the documentation requirements in the regulations is not to satisfy the regulators, but to preserve the public trust in research.

9 Summary

To quote from the publication "Preserving the Public Trust" prepared by the Institute of Medicine, "The complex system that sustains research is ultimately premised on trust – trust in the people and organizations that conduct research. In the wake of revelations about lapses in research ethics, such trust must be earned…"

The evolution of the currently regulatory process governing human subjects research is based on preservation of the public trust by establishing standards for the ethical conduct of human subjects research and requirements to ensure the accountability of researchers engaged in such research.

The IRB review system is designed to provide an independent, objective review of research involving human subjects so that the privilege of conducting human subjects research may be maintained.

Informed Consent

1 Goals

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

- Comprehend the underlying ethical requirements of informed consent
- Describe the eight basic elements and the six additional elements of informed consent
- Illustrate the appropriate method of documenting informed consent
- Define the special circumstances and requirements associated with obtaining the informed consent of vulnerable populations for participation in research
- Describe the conditions under which obtaining and/or documenting the subject's consent may be waived

2 Introduction

Becoming involved in human research is an undertaking that requires serious thought and commitment on the part of the researcher as well as the willing participant.

The desire to gain scientific knowledge through human subject research must be balanced with ethical concerns at all times.

Participants must be provided information regarding the nature of the research as well as risks, benefits and expected outcomes. This should be communicated during a dialogue (the informed consent "process") as well as in writing (the informed consent "document").

The participants must be fully informed before agreeing to enroll in a research project and kept updated on new information that becomes available that might affect their willingness to continue participation.

3 Informed Consent Process

Informed consent is the primary ethical requirement and foundation of human subject research. It reflects the basic principle of respect for persons.

In addition to being the morally correct thing to do, obtaining informed consent of subjects is required by Federal law and University policy. Failure to obtain proper informed consent may result in revocation of research funding, disbarment or criminal prosecution at the Federal level and sanctions ranging from reprimand to dismissal by the University. Investigators may also be subject to civil suits arising from violations of Federal law and/or University policy. The University is not obligated to defend an investigator if laws or policies were violated.

It should always be remembered that providing information and educating the subject is not a single event but an ongoing process. The informed consent process is designed to provide prospective subjects with all relevant information so that they can decide whether or not to participate. Investigators have a contractual and ethical responsibility to keep research subjects fully informed of any new information that might affect their willingness to continue study participation. The process should permit the potential research subject to ask questions and to exchange information freely with the study investigators.

No investigator may involve an individual in a research study unless the investigator has prospectively obtained the legally effective, written informed consent of the individual or the individual's legally authorized representative (unless the IRB has specifically granted a waiver of the consent process or the requirement for written informed consent). See section on "Waiver of Informed Consent" which is addressed later in this chapter.

The investigator must seek informed consent under circumstances that give the individual sufficient time to consider whether or not to participate in the research study and that minimize possible coercion or undue influence.

Informed consent to participate in a research study should be sought at a time separate from obtaining informed consent required for standard medical care/treatment purposes. Participants might be overwhelmed with forms to sign for their medical care and not realize that they are agreeing to participate in research.

4 Basic Elements of Informed Consent

Both the FDA regulations (Title 21 Part 50) and the Federal Policy regulations (Title 45 Part 46.116) outline the requirements for obtaining and documenting informed consent.

Both define the eight basic elements of informed consent that must be included in the informed consent document. They are as follows:

4.1 A statement that the study involves research.

This description/statement should include information such as:

- An explanation of the purpose of the research
- The reason why the potential subject is being asked to participate

- The expected duration of study participation
- A description of the procedures that will be performed
- Identification of any procedures which are experimental.

It is important to explicitly state that the individual is being asked to participate in a research study so as to clearly differentiate:

- The relationship between patient-physician from the relationship between subject-investigator; and
- Informed consent for participation in research from informed consent for invasive clinical procedures.

The consent process (and document) must clearly describe all of the procedures that will be performed for research purposes. Procedures that are experimental should be clearly distinguished from standard medical procedures used for screening or follow-up.

Procedures that are performed solely as part of the subject's routine medical care should not be included.

4.2 A description of any reasonably foreseeable risks or discomforts.

The risks of all procedures performed for the purpose of the research should be explained. The explanation of risks should be communicated in such a way that the information is honest, factual and does not minimize reported adverse effects. Statements should not imply that an experimental intervention is safe when the purpose of the study involves a determination of safety.

Risks of all medications should be outlined, including risks of approved drugs that will be administered to facilitate a research procedure. For example, if a commonly used topical anesthetic will be used, e.g., lidocaine, in order to implement a study procedure, the risks of lidocaine must be addressed.

The subject should be provided with information that addresses not only the nature and severity of the risks, but also their expected frequency.

4.3 A description of any benefits to research subjects or to others that may reasonably be expected from the research.

The description of potential benefits should be clear and not overstated. If there is no potential for direct benefit to the research subject, this should be explicitly declared. If applicable, it may be stated that future patients who are afflicted with this same problem might benefit from the current research. Statements should not imply that an

experimental intervention is effective when the purpose of the study is to evaluate its effectiveness.

Note: Remuneration for participation in research study is not considered a benefit. Remuneration should be addressed in the Costs and Payments section of the consent form.

4.4 A disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the potential research subject.

To enable a rational choice to participate in a research study, potential research subjects must be aware of the full range of treatment options. Thus, the informed consent discussion (and document) should briefly address any treatments currently available as alternatives to study participation. For many research studies, the only alternative to study participation is not to participate and this should also be stated in the consent form document.

4.5 A statement describing the extent to which confidentiality of records identifying the subject will be maintained

The subject should be informed of measures in place to protect their privacy and the confidentiality of research data, e.g., using identity codes instead of names, storing files in locked cabinets and protecting computerized information with passwords.

If records will be maintained in such a manner that it might be possible to link the results of the study with subject identifiers, this must be explicitly stated. If any other entity, such as the sponsor of the research study, an applicable regulatory agency (e.g., FDA or OHRP), and/or hospital billing departments, requires access to the study records, the potential research subjects must be so informed. Additionally, a statement should be included that the Research Conduct and Compliance Office of the University of Pittsburgh may audit the research study records for quality assurance purposes.

Any possible exceptions to maintaining confidentiality of the research records should also be addressed (e.g., required reporting of child or elder abuse and subpoena of records by the court).

In cases where data are being collected about sensitive issues such as illegal behavior, alcohol abuse, drug abuse, sexual practices or genetic information, a Federal Certificate of Confidentiality may be obtained. These certificates are designed to protect data from the possibility of subpoena by the courts. Certificates are issued sparingly and are appropriate only when the research information gathered is of a sensitive nature and protection is deemed necessary to achieve the research objectives while protecting the study subjects' confidentiality and privacy.

4.6 For research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatments are available if injury occurs; and, if so, what they involve, or where further information may be obtained.

This explanation may be omitted from the informed consent document for minimal risk protocols (e.g., psychosocial studies) where injury associated with study participation is unlikely.

4.7 A statement that participation is voluntary; that refusal to participate will involve no penalty or loss of benefits to which the potential research subject is otherwise entitled; and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the research study involves patients, the statement should specify that refusal to participate in or withdrawal from the research study will have no effect on the individual's current or future care at a UPMC facility. Likewise, if the research study involves recruiting primarily University students, the statement should specify that refusal or withdrawal would not affect current or future academic standing.

4.8 An explanation of whom to contact for answers to pertinent questions about the research and the rights of research subjects, and whom to contact in the event of a research-related injury to the subject.

The Voluntary Consent Statement should explain that the subjects should contact the principal investigator or a member of the research staff with questions regarding any aspect of the study. The first page of the consent form must list the principal investigator and all co-investigators. Include either an address and phone number for each listed investigator or a common departmental address and phone number, if applicable.

For studies with risk of physical harm, emergency contact information must be provided on the first page of the consent document. The subject must be able to reach a member of the research team within two phone calls at any time. Therefore, emergency instructions must be provided on audex messages and a "real person" must answer and triage the call to the research team who is familiar with the protocol and study intervention. Note that it is unacceptable to have a "physician on call" who is not familiar with the protocol address the call.

The number for the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668), should also be included in the Voluntary Consent Statement.

The Compensation for Injury Section should instruct the subjects that, if they believe they have been injured as a result of the research procedures, they are to notify the principal investigator.

5 Six Additional Elements of Informed Consent

In addition to the required eight basic elements of informed consent, six additional elements should be communicated to the subject and addressed in the consent form, if applicable to the design of the study

5.1 The approximate number of subjects to be involved in the study.

If the number of subjects in a study is material to the individual's decision to participate, the potential research subjects should be told not only the approximate number of subjects involved in the study but also why this information is important. For example, a Phase I study may involve a few individuals who are the first human subjects to receive the investigational agent. This information might be significant in making the decision to participate.

5.2 A statement that the particular treatment or procedure might involve risks to the subject (or to the embryo or fetus, if the subject is pregnant or becomes pregnant) that are currently unforeseeable.

Investigators should ensure that individuals who agree to enter a study fully understand the potential risks that the study poses. Potential research subjects, both women and men, need to understand the danger of receiving any investigational agent, of which effects on the fetus are unknown. If measures to prevent pregnancy are warranted, contraception should be fully explained.

5.3 Anticipated circumstances under which a subject's participation might be terminated by the investigator without regard to the individual's consent.

Examples of specific reasons for termination by the investigator should be provided, i.e.,

- Deleterious effect of participation on the subject's health or welfare,
- Failure to comply with instructions to effectively implement study activity, and/or
- Failure to maintain appointment schedule.

5.4 The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

When withdrawal from a research study might have deleterious effects on the subject's health or welfare, the informed consent document should explain any withdrawal procedures that are necessary for the subject's safety and welfare. For example, gradual

discontinuation of a medication and monitoring during the weaning process might be indicated rather than an abrupt discontinuation of the drug. Another example might be a subject's decision to terminate an investigational life-sustaining device. In this case, the possibility of death as a result of his or her decision must be clearly explained.

5.5 A statement that significant new findings developed during the course of the research which might relate to the subject's willingness to continue participation will be provided to the subject.

This statement might not be applicable to certain research studies (e.g., psychosocial studies) and may be omitted from the respective informed consent document. However, if the study involves an investigational drug or device, any new information about additional side effects that are revealed during the course of the study must be communicated to the enrolled subjects.

- For subjects already enrolled and actively participating in a research study, new information may be communicated via a written consent form addendum. This addendum is an abbreviated form that specifically addresses the new information. It also should contain a reiteration of the voluntary consent and right-to-withdraw statements and must be signed by the subject or subject's legally authorized representative and the person obtaining the consent. It must be submitted and approved by the IRB prior to implementation. Once implemented and signed, the addendum should be filed with the original consent form, a copy given to the subject and a copy placed in the subject's medical chart if hospitalized.

- For prospective new subjects, the previously approved consent form and protocol should be modified to integrate the new information.

- All modifications to the protocol, consent form document, and addenda must be submitted and approved by the IRB prior to their implementation.

5.6 Any additional costs to the subject that might result from participation in the research.

Potential research subjects should be clearly informed if they, or their third-party insurance providers, will be billed for any procedures associated with their participation in the research study.

Potential research subjects should also be informed that certain third-party insurance providers might not fund care that is delivered as part of a research study and that, under such circumstances, the subjects will be held directly accountable for the charges.

6 Important Points to Remember

- Information given to potential research subjects must be understandable to them. Technical and medical terminology should be avoided or, if used, explained in lay terms. Short and concise sentences are often most effective. Acronyms should be spelled out in full the first time they are used. It is helpful to have an individual unfamiliar with the research area read and comment on the consent form prior to submitting it for IRB approval.

- Deferred consent is not permitted. This means that obtaining informed consent may not be postponed to a time after research activities or screening procedures have already been performed.

- Phone consent is not permitted. (Please refer to the section on Waiver of Informed Consent and Waiver to Document Informed Consent for possible exceptions to this rule.)

- The principal investigator must retain the original signed informed consent document in the research records. A copy of the informed consent document must be given to the research subject or subject's legal representative. For hospitalized subjects, a copy of the signed informed consent document must also be included in the subject's medical chart.

- The informed consent document may not include exculpatory language through which the potential research subject is made to waive or appear to waive any legal rights or releases, or appears to release the investigator, the sponsor, the institution or their agents from liability for negligence.

- The investigator should establish procedures to ensure that only the current IRB-approved version of the consent form is being used.

- Informed consent is an ongoing process and subjects must be kept informed of any new information that may influence their decision to continue study participation.

7 Documentation of Informed Consent

It is the policy of the University of Pittsburgh IRB that the subject or the subject's legal representative and the person obtaining their consent must sign the consent form document.

Note that, if the study involves a drug, device or surgical procedure, the person obtaining the consent must be an investigator listed on the first page of the consent document who is also an appropriately credentialed physician.

All individuals must sign and date the consent form in their own hand. No one may date the signature of another.

If a legal representative signs the consent form, the relationship to the subject should also be documented.

To ensure that the subject (or subject's legal representative) has read and discussed each page, a space should be provided on the bottom right-hand corner of every page of the consent form for the subject (or legal representative) to initial. Initials are not required on the signature page.

It is good clinical practice to include a progress note in the subject's case history that the subject has been properly informed of the details of study participation. This note should include highlights of the consent process dialogue and include:

- who was present for the discussion
- that the risks were presented and discussed
- that all questions were answered
- that the subject appears to understand the conditions of the study and agrees to participate by signing the informed consent document.

This note should be signed and dated by the person making the entry. It is also good clinical practice to include in the narrative note the "time" that consent was obtained, especially if research procedures will be performed on the same day.

7.1 Verification of Explanation

In cases where assent is obtained from children or from adult subjects who are decisionally impaired but capable of executing some judgment of the nature of the research and their participation in it, a statement should be included in the subject's progress notes or medical record to indicate that the investigator has discussed the study in detail with the subject, answered all questions, and that the subject has provided affirmative agreement (i.e., assent) to participate in this research study. Any child or decisionally impaired adult who is able to provide a signature may sign an assent statement.

7.2 Parental Certification

In cases where minor subjects are to be enrolled in a research study, the parent(s) or legal guardian(s) must also sign the consent form agreeing to allow the child to participate. The IRB has the authority to determine if one or both parents must sign for a minor child.

7.3 Witness Signature

A witness signature is required when the prospective subject is physically unable to sign the consent document. In those instances, the subject should "make their mark" and a witness must sign verifying that the named individual made the mark.

Note that a witness signature is also required when enrolling non-English speaking subjects or decisionally impaired adults. This will be addressed in the applicable sections.

Refer to the IRB Reference Manual, Chapter 8, for more detailed information regarding required signatures.

8 Screening Tests and Interviews Prior to Subject Enrollment

Screening procedures (including interviews) that are performed solely for the purpose of determining if individuals are eligible for participation in a research protocol are subject to regulations governing human subject protections, including the requirement for written informed consent.

With respect to screening interviews/surveys, written informed consent must be obtained prior to conducting the interview/survey if:

- the interview/survey is being performed for research purposes;
- the recorded responses to the interview/survey could place the individual at risk of civil or criminal liability or be potentially damaging to his/her employability, insurability, or reputation; and
- subject identifiers are retained with the recorded interview/survey responses.

If a separate consent for "screening procedures" is prepared, it must include the eight basic elements of informed consent.

Note that for "phone" screening interviews, a waiver for "written" informed consent may be granted by the IRB with appropriate justification and documentation. See the section on “Waivers” later in this chapter.

Medically proven and accepted procedures that are performed for the standard clinical care of a prospective research subject and which would have been performed whether or not study entry was contemplated (e.g., procedures consistent with the diagnosis or treatment of a disease or medical condition) may be performed and the results subsequently used for determining research study eligibility. However, the protocol and consent document must indicate that historical medical information will be documented in the research records.

9 Informed Consent of Non-English Speaking Subjects

Research subjects who do not speak English should be provided with a "short form" consent document, written in the subject's native language, that summarizes the basic elements of informed consent. (Copies of such "short form" consent documents, translated into several commonly encountered foreign languages are available from the IRB Office.)

The standard (i.e., IRB-approved, full-description) informed consent document should be presented verbally to the subject in his/her native language and all questions answered. UPMC maintains a staff of interpreters that may assist with this interaction. The International Patient Relations Center may be contacted by calling 412-648-6262. Be advised that arrangements with this office must be made well in advance of subject enrollment.

When enrolling a non-English speaking subject, consideration and arrangements should be made for communication with the subject for the consent process as well as throughout the course of the research study. The consent process for this population must be witnessed and the collection of accurate information regarding the subject's status and recording of adverse events is imperative.

Refer to the IRB Reference Manual, Chapter 6, and contact the IRB for guidance if the study involves a non-English speaking population or subject.

10 Informed Consent of Vulnerable Populations

10.1 Children as Research Subjects

In Pennsylvania, children are defined as persons < 18 years of age who have not attained the legal age or status to consent for treatment or procedures involved in research.

Note that the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects, effective October 1998, requires that children be included in all human subject research conducted or supported by the NIH unless there are scientific and ethical reasons not to involve them.

When enrolling children into a protocol, the consent of one or both parents or guardians must be obtained as well as the assent of the child.

Under Pennsylvania law, neither foster parents nor Children and Youth Services (CYS) may provide the informed consent to enroll a foster child in a research study. Only the birth parent or a person adjudicated as an adoptive parent can provide consent.

If a legal guardian provides consent, the court order or legal authorization should be copied and included in the research records with the consent document.

For detailed instructions pertinent to the enrollment of children, the requirements and exceptions, please refer to the IRB Reference Manual, Chapter 6, and/or 45 Part 46, Subpart D at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd

10.2 Pregnant Women and Fetuses

Special research protections for pregnant women and fetuses have been in existence since 1975. The informed consent of the pregnant woman should be obtained in accord with the standard regulatory provisions for informed consent if the research hold out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit to both the pregnant woman and the fetus, or no prospect of direct benefit for the pregnant woman nor fetus when the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means.

The informed consent of the pregnant woman and the father shall be obtained in accord with the standard regulatory provisions for informed consent if the research holds out the prospect of direct benefit solely to the fetus; except the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity, or if the pregnancy results from rape or incest.

For detailed instructions pertinent to the enrollment of pregnant women and fetuses, pregnant children or research involving neonates, please refer to the IRB Reference Manual, Chapter 6 and/or 45 Part 46, Subpart B at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartb

10.3 Prisoners

The IRB committee reviewing and approving a protocol that will include prisoners must include a prisoner representative. Once the protocol is approved by the IRB and Department of Health and Human Services (DHHS), prisoners enrolled in the research must provide informed consent. Prisoners enrolled in research must also be informed that their participation will have no effect on their parole.

If a research subject becomes incarcerated during his/her participation in a study, the IRB must be notified immediately. The subject may be withdrawn with full disclosure of the reason for such action or the protocol must be resubmitted to the IRB. The IRB will re-review the protocol in accordance with the listed requirements for research involving prisoners.

For detailed instructions pertinent to the enrollment of prisoners, please refer to IRB Reference Manual, Chapter 6, and/or 45 Part 46, Subpart C at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc

10.4 Persons with Decisional Impairment

As a general rule, all adults, regardless of their diagnosis or condition, should be presumed competent to consent unless there is evidence of serious mental disability that would impair reasoning or judgment. Mental illness or cognitive impairment alone should not disqualify a person from consenting to participate in research; rather, there should be specific evidence of the individual's incapacity to understand and to make a choice before being deemed unable to consent.

If the research is determined to involve greater than minimal risk and does not provide direct benefit to the participant, the research must bear some direct relationship to the cause of the subject's decisional impairment, i.e., Alzheimer's disease. The need for proxy consent must be justified and the methods in place to obtain proxy consent must be explained in the protocol. The IRB may require additional safeguards where appropriate for a given protocol.

The individual who may sign as the subject's legally authorized representative reflects Pennsylvania State Law and details may be found in the IRB Reference Manual, Chapter 6.

If a person with decisional impairment is capable of exercising some judgment concerning the nature of the research and their involvement, the investigator should obtain the subject's assent in addition to the consent of the legally authorized representative. The subject's verbal objection to participate is binding and the subject must not be enrolled.

Note that the proxy consent and assent of a decisionally impaired adult must be witnessed and the consent document signed by the witness.

A narrative note describing details and circumstances of obtaining proxy consent should be documented in the research records. Please refer to the IRB Reference Manual, Chapter 6, for further guidance when the research involves decisionally impaired adults.

10.5 Traumatized and Comatose Persons

Research involving patients undergoing emergency care differs from clinical research in other settings because the patient's capacity to provide consent is often severely compromised, and decisions about participation in research might have to be made too quickly to obtain permission from the patient's legally authorized representative.

In these cases, a waiver of informed consent may be necessary. Please refer to the section of this chapter that addresses "Waiver of Informed Consent for Research Involving Emergency Care" or to the IRB Reference Manual, Chapter 6.

If the subject recovers and is capable of making a decision, the research study must be explained to him/her (informed consent process), and s/he must provide his/her written informed consent to remain in the study.

10.6 Terminally Ill Patients

Research involving terminally ill patients presents additional concerns in that potential subjects tend to be more vulnerable to coercion or undue influence, and the research is likely to present greater than minimal risk. As a result, special attention should be given to the informed consent process. The following elements must be emphasized:

- Accurate information concerning eligibility for participation (i.e., diagnosis and prognosis) and risks and benefits should be conveyed clearly and in a manner that will not either engender false hope or eliminate all hope.

- Patients should be fully informed of the availability of treatment alternatives, including at what point their participation in the research study should or might be terminated to permit a treatment alternative (e.g., discontinuation of participation in a drug trial to permit organ transplantation), and information that another alternative might be no additional treatment.

- Any costs to the subject associated with research study participation should be stated explicitly.

11 Waiver of Consent

There are circumstances in which an investigator may petition the IRB to waive the requirement for informed consent or for documentation of informed consent. The categories of studies and the requirements for each are described below.

11.1 Waiver of Informed Consent for Minimal Risk Research Studies

The IRB can approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or may waive the requirement to obtain informed consent provided that each of the following criteria is met:

1. The research involves no more than minimal risk to the subjects.
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
3. The research could not practicably be carried out without the waiver or alteration.
4. Whenever appropriate, the subjects will be provided with additional pertinent information after enrollment.

An example of a research protocol that meets these criteria would be a study that involves surveys and questionnaires presented to adolescent subjects being seen at a clinic that provides information and treatment for sexually transmitted diseases. For research studies, enrollment of children under the age of 18 requires parental consent. However, in this case, a waiver of the requirement for parental consent may be appropriately justified based on the fact that the State of Pennsylvania permits adolescents to seek treatment and education regarding sexually transmitted diseases without their parents' consent. To require consent of the parents for the adolescent's participation in the research study would result in a disclosure of his/her attendance at the clinic and would be in opposition to the State's policies.

To be considered for such a waiver, the principal investigator must address each of the above criteria, including a justification of its applicability to the proposed research. This information should be included in the recruitment section of the IRB protocol as well as in a cover letter. Be advised that the full Institutional Review Board reviews all requests for a waiver of consent. These requests are considered seriously and must have indisputable justification before a waiver can be granted.

11.2 Waiver of Informed Consent for Research Involving Emergency Care

The Federal Policy and FDA regulations permit individuals to be enrolled, without their legally effective informed consent (or the consent of their authorized representatives), in research studies directed at the evaluation of emergency care interventions provided that certain basic conditions are met:

1. Potential subjects are in a life-threatening situation and:

    - available treatments are unproven or unsatisfactory; and
    - collection of scientific data is required to determine the safety and effectiveness of the experimental intervention.

2. Obtaining informed consent is not feasible because:

    - the potential subject is not able to consent due to his/her medical condition;
    - the intervention must be administered before consent from the potential subject's authorized representative is feasible
    - there is no reasonable way to prospectively identify potential eligible subjects.

3. Participation in the research study holds the prospect of <u>direct</u> benefit to the subjects because:

    - the subjects are facing a life-threatening situation;
    - appropriate pre-clinical and prior clinical research studies support the potential for direct benefit; and
    - the risks associated with the research are reasonable relative to the risks of the subjects' condition and the risk/benefit ratio of standard therapy for the condition.

4. The research could not be practicably carried out without the waiver.

In addition to meeting the above basic conditions, there are multiple additional requirements that must be addressed before the IRB can grant a waiver of the informed consent requirement for research involving emergency care procedures. Investigators involved in the implementation of such research studies, wherein a waiver of informed consent is an anticipated necessity, are advised to engage the assistance of the IRB Office as early as possible in the implementation process.

11.3 Waiver of Requirement to Obtain a Signed Informed Consent Document

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if either:

1. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality;

2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

    Note: If a waiver is granted based on this criterion, each subject must be asked whether s/he wants documentation linking her/him with the research, and the subject's wishes will govern.

To be considered for such a waiver, the principal investigator must address, in the recruitment section of the IRB protocol submission, the criterion under which s/he is requesting the waiver and provide a justification of its applicability to the proposed research.

Note that if the IRB grants a waiver of the requirement to obtain a signed consent form, this does not eliminate the requirement to obtain the informed consent of the subject for study participation. Thus, accompanying this waiver request should be a script of the information that will be provided to potential subjects in obtaining their verbal consent for study participation. This verbal consent process should include all of the basic and additional, applicable elements of informed consent. The waiver request should also address the mechanism that will be used by the investigators to document that the verbal consent of subjects has, in fact, been obtained.

This process is frequently used for the initial phone screening for prospective subjects. The phone screening presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. To apply for a waiver to document consent for the phone screening, the investigator must justify the request, include a script that includes the eight basic elements of consent and provide the list of screening questions that will be presented to the prospective subject during the phone screening,

Refer to the IRB Reference Manual, Chapter 8, for additional guidance.

12 Additional Waivers

It is possible to obtain waivers of consent for other research endeavors. For example, a researcher may apply for a:

- Waiver of consent when performing record review that is "preparatory to research"

- Waiver of consent to use medical records information (PHI) when the researcher is also the health care provider for the prospective subject
- Waiver of the HIPAA Authorization for sharing contact information for the purpose of recruiting subjects
- Waiver for the retrospective review of medical records.

Please refer to the IRB Reference Manual, Chapter 8, for details regarding the necessary justification and documentation requirements to apply for any of these waivers.

PRINCIPAL INVESTIGATOR RESPONSIBILITIES AND DOCUMENTATION

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 later in this chapter.)

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 involved in the study allowing 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 and contact 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.

Additionally, a note should be included in the research record that explains why the change is necessary and that the individual making the change is authorized to do so. Ideally, any change should be made by the person who made the original entry or 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 six years following study completion or discontinuation or upon written notification from the sponsor that the files may be destroyed, whichever comes last.

10 Unanticipated Problems and Adverse Events

Overview:

Federal regulations at 45 CFR 46.103(b)5) and 21 CFR 56.108(b) require IRBs to have written procedures for ensuring prompt reporting to the IRB of any unanticipated problems involving risks to subjects or others. Consistent with these regulations and IRB policies, investigators are required to report such unanticipated problems (which may also be adverse events) as they occur.

The Office for Human Research Protection (OHRP) considers unanticipated problems, in general, to include any incident, experience or outcome that meets all of the following criteria:

- Is unexpected in nature, severity or frequency
- Is related or possibly related to a subject's participation in the research
- Places subjects or others at a greater risk of harm (physical, psychological, economic, or social harm) than was previously known or recognized

Unanticipated problems may include adverse events if they meet the stated criteria (noted above). As described in the OHRP guidance, only a small subset of adverse events occurring in human subjects participating in research will meet these criteria for an unanticipated problem. The vast majority of adverse events will not meet these criteria and therefore do not meet reporting guidelines.

A. Adverse Events

1. **Internal** adverse events must be reported if they meet the following criteria
    i. Unexpected
    ii. Related or possibly related to research participation
    iii. Serious

2. **External** adverse events must be reported if they meet the following criteria:
    i. Unexpected
    ii. Related to research participation
    iii. Serious AND suggests that the research places the subject or others at greater risk than was previously recognized

The following definitions apply to determine what is reportable.

Adverse event: An unfavorable medical occurrence, which may include abnormal signs (for example, abnormal physical exam or laboratory finding), symptoms, or disease, temporally associated with, but not necessarily considered related to, the subject's participation in the research study.

Internal adverse event: An adverse event that occurs at the University, UPMC, or other site that falls directly under the authority of the University IRB.

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

Serious adverse event: An adverse event that meets one or more of the following criteria:

1. is fatal or life-threatening
2. requires or prolongs hospitalization
3. results in a persistent or significant disability/incapacity
4. results in a congenital anomaly/birth defect
5. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Unexpected: Not identified by nature, severity or frequency in the current University IRB-approved research protocol or informed consent document.

Possibly related to the research intervention: In the opinion of the principal investigator, there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the procedures involved in the research.

Related to the research intervention: In the opinion of the principal investigator, the incident, experience or outcome more likely than not was caused by the procedures involved in the research.

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 of a trial (IND or IDE), the investigator assumes the responsibility for directly notifying the FDA of adverse events. The FDA Medwatch Form is typically used for reporting. http://www.fda.gov/medwatch/getforms.htm

- Adverse events occurring in UPMC facilities may also need to be reported to Risk Management through the RiskMaster program. See the adverse event reporting policies for the specific UPMC hospitals at: http://patientsafety.infonet.upmc.com/

B. "Other" Unanticipated Problems

This category applies to unanticipated problems involving risk to human subjects or others that are NOT adverse events. The following are examples of reportable problems.

- any deviation from an IRB approved protocol that involves risk to subjects or has the potential to recur (e.g., over enrollment, incorrect dosing or labeling)
- any deviation from the protocol implemented to eliminate an apparent or immediate hazard to a subject without prior IRB approval
- any publication, safety monitoring report, interim result or other finding that indicates an unexpected increase in the risk to benefit ratio
- subject complaints that indicate an unanticipated risk that cannot be resolved by the research staff
- any untoward event that affects the welfare or the privacy, confidentiality or other rights of research subjects or members of their family (e.g., lost or stolen research data)
- any other untoward event that presents a risk to investigators and/or research staff involved in the conduct of the research.

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

The following table summarizes the requirements and time frames for reporting to the IRB adverse events or unanticipated problems that meet the reporting requirements.

Event Criteria (must meet all)	Reporting Time Table
Internal adverse event that is: ▪ Unexpected ▪ Fatal or life-threatening, and ▪ Related or possibly related to the research intervention	Within 24 hours
Internal adverse event that is: ▪ Unexpected ▪ Serious but not fatal or life-threatening, and ▪ Related or possibly related to the research intervention	Within 5 working days
External adverse event that is: ▪ Unexpected ▪ Serious ▪ Related to the research intervention and ▪ Suggests that the research places the subject or others at greater risk than was previously recognized.	Within 30 working days
All other unanticipated problems involving risks to human subjects or others	As soon as possible

11 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.

12 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.

13 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).

14 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).

15 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 the training titled Research Integrity is dedicated to the Conflict of Interest issue.

16 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.coi.pitt.edu.

Research involving Records

1 Introduction

Scientific investigators have made many contributions to knowledge, medical practice, and public policy, by collecting information from various kinds of records. These sources include medical records, motor vehicle records, criminal justice records, and school records.

Most of these records at one time existed only on paper. However, many now also exist in the form of computerized databases, which have greatly facilitated research but have also raised additional privacy concerns. Each person conducting scientific research based on records should:

- **Understand concerns about inappropriate access and unauthorized disclosure.**
- **Have procedures in place to protect the confidentiality of the records while in use and of the information collected.**
- **Obtain all required approvals (institutional, state, federal, and international, if applicable) prior to conducting the research.**

Before collecting information from records for purposes of research, an investigator should consult with the Institutional Review Board (IRB) at his/her own institution. He/she should also contact the appropriate administrator at the institution where the records are owned or maintained.

2 Risks of Records-Based Research

These risks concern privacy and confidentiality. Risks stem from the possibility that disclosure of the information could reasonably:

- Place the subject at risk of criminal or civil liability.
- Be damaging to the subject's financial standing, employability, or reputation.

Some records studies involve data collection only from existing records, while other research may combine data collected from records along with data obtained directly from subjects. The risk level may be increased when a study has multiple avenues of data collection.

The IRB will carefully review the procedures that are in place to protect the confidentiality of the information being collected. Investigators are generally

asked to describe who will have access to identifiable private information and how inadvertent disclosure will be prevented.

3 Privacy/Confidentiality

3.1 Privacy

Privacy generally means the state of being free from intrusion into one's personal life. In the context of recorded information, it refers to an expectation or, in some cases, a legal right of a person to control access to personal information about himself/herself.

3.2 Confidentiality

Confidentiality is an ethical principle, generally based on trust, that personal information will be kept secret, unless the person about whom the information has been collected permits disclosure or unless disclosure is warranted for exceptional circumstances, such as to prevent a harm.

3.3 Balance

Research using records must balance access to information in the service of important societal goals with the need to protect sensitive information about the health or behavioral characteristics of individuals. Information about a particular person, if disclosed inappropriately or in the wrong context as a result of research, could be harmful to that individual. Consider the following possible scenarios:

- A person could be ostracized if community members learned that he or she had - been accused of partner abuse.
- A parent could punish a minor child if he/she discovered that the teenager was sexually active.
- A person's chance for a promotion at work could be damaged by the discovery that he/she has a psychiatric diagnosis, heart disease, cancer, or some other medical condition.

4 Minimizing Risks

Three important components of minimizing risks in records-based research are:

- **Respect for Persons,** which concerns the rights of individuals to decide how confidential information will be used and disclosed,

- **Integrity**, which pertains to the conduct and ethics of study investigators, research staff, and institutional staff,

- **Security**, which focuses on the protection of data and people from inappropriate access or actions.

4.1 Respect for Persons

Individual privacy can be most completely protected by obtaining the consent of the research subjects and by using data collection and security procedures that are very stringent. When consent is obtained, the subject whose data will be used has an opportunity to learn how the information about him/her will be used and how it will be protected. Through the consent process, the investigator can describe directly to the research subject the extent to which confidentiality---safeguarding information based on trust---will be maintained. The research subject can then decide if he/she will permit the use of information about himself/herself.

4.2 Research Integrity

In some cases, it may not be possible to contact and obtain consent from all the individuals whose information is needed for a particular research effort. Some records-based research may need to use thousands of medical records, for instance, when rare adverse events of a particular medication are the subject of a study. If an IRB agrees that obtaining consent of the research subjects is not feasible and determines that all federally required conditions have been met, the IRB will approve research only if when it includes very clear data security procedures. Because virtually all kinds of information in records used in research could be harmful if inadvertently or improperly disclosed, it is important to ensure that all information collected for research purposes has equally strong protections. When an IRB has determined that it is not practicable to obtain consent and the risks of the research are reasonable in relation to the potential benefits of the research, the investigator describes confidentiality protections to the IRB, rather than directly to the subject. In a sense, the trust relationship is then between the investigator and the IRB, who represents the research subject. Therefore, it is important for IRB applications to provide information about the training and experience of investigators and research staff to document knowledge of procedures that will protect the research subject.

4.3 Security

Federal regulations *require* that IRBs approve only research projects that are designed to minimize risks. *Therefore*, following the institution's procedures, the IRB will review data security procedures so as to assess the following:

- What kind of identifying information will be collected?
- Who will have access to the identifying information and the research data?
- What kinds of codes or encryption will be used to separate research data from subject identifiers?
- How will limitations on access be ensured?
- How will research staff persons be trained about privacy and confidentiality?
- Will research staff be required to sign an oath of confidentiality?
- How long will identifiable information or linkages to personal identifiers be kept?
- For data being transmitted physically and/or electronically, what encryption methods will be used?
- What procedures will be used for disposal/destruction of documents?

Although IRBs assess these same protections as part of their review of all research studies, records-based studies often present a particular challenge because of the possibilities of utilizing and linking various data sources.

5 Categories of IRB Review: Full IRB Review or Expedited IRB Review?

Some IRBs may review records-based research using an *expedited* process and some may require *full* board review. A full IRB review is done at a convened meeting of the IRB membership, while a Chair or one or more experienced IRB members designated by the Chair may conduct an expedited review.

Many IRBs consider most record review studies to be "minimal risk", and therefore, they may be reviewed using an expedited process. However, each institution may consider the following in determining which studies present minimal risks to subjects:

- What is the nature and sensitivity of the data?
- What data, if disclosed outside the research setting, might cause harms?
- What study procedures, such as encryption methods, will be in place?
- How experienced are the investigators and their staff?

Also, each institution may have a different procedure for deciding whether full or expedited review is required and perhaps a different application form for minimal risk studies. Be sure to check with the IRB where you are requesting review to find out what type of review is required for your records study.
Investigators should remember that, in this context, "expedited" does not necessarily mean "quick." Research applications may need to be mailed to one or more IRB members, after which the reviewers may recommend that the IRB

Chair approve the study or that it be reviewed at a full IRB meeting. Research may not be disapproved using an expedited process, so, in some cases, review may be delayed because a project is forwarded to a full IRB meeting.

6 Records-based research that may be eligible for an application for exemption

Generally, an IRB must review and approve all research that includes review or collection of existing data, documents, or records relating to identifiable human subjects. However, there are some instances in which such research is exempt from the federal regulations (45 CFR 46). Records research can be certified by an institution or IRB office as exempt when:

- The sources of information are publicly available or
- The information collected is recorded by the investigator in such a way that the subjects cannot be identified, directly or indirectly, through identifiers linked to the subjects.

Research conducted solely with publicly available data are exempt, unless the institution has a policy to the contrary. Publicly available data must be truly publicly available to anyone, regardless of an individual's status as a researcher. For example, publicly available data may be available for purchase.

In order for research using records to meet criteria for exemption according to 45 CFR 46 101b, the records must already be "existing," i.e., the information in the records must have been collected already. *If the investigator will be able to identify the subjects directly from his/her research records, the research cannot be considered exempt from review.* An investigator may maintain a mechanism for identifying subjects (e.g., keeping the subjects' names or other identifying information or keeping a "crosswalk" between a study number and a person's name or other identifier). Most institutions would not consider research with this kind of indirect link to identifiers to be exempt. However, in some cases, when the investigator does not have access to identifying information on the subjects, research may be declared exempt by an institution or IRB if a signed agreement is in place between the investigator and the original record holder stating that identifiers will never be given to the investigator.

Even if a study meets the federal requirements for exemption, it might not be considered exempt according to institutional policy or state law. Describing your study procedures in writing in accordance with institutional requirements is the best way to find out whether IRB review is required at your institution.
The most important point to remember about "exempt research" is that a determination of exemption must be made at the institutional level in accordance with institutional policies.

Most institutions have a procedure by which an investigator can request a Certificate of Exemption or receive a written certification that the institution has determined that the research is not subject to 45 CFR 46. OHRP has provided guidance on this issue.

7 Consent Requirements

Consent/Authorization or Waiver of Consent?
For all research, including records-based research, the investigator must obtain the consent of the subject unless the IRB has determined that it will approve a waiver of consent. According to DHHS regulations, informed consent from the subject must be obtained unless all of the following conditions are found and documented:

- The research involves no more than minimal risk to subjects.
- The rights and welfare of the subjects won't be adversely affected by the waiver of consent.
- The research could not practicably be carried out without the waiver of consent.
- When ever appropriate, the subjects will be provided with pertinent information after participation.

In addition, the HIPAA Privacy Rule requires a written authorization from subjects for use of their protected health information, unless an IRB approves a waiver of authorization based on similar criteria to those listed above (see the "HIPAA and Human Subjects Research" Module for more information about HIPAA requirements).

Most IRB applications require that an investigator who is requesting a waiver of consent provide a written justification for this. This justification should address both the requirements of 45 CFR 46 and of HIPAA, and any additional requirements of state law and institutional policies. In assessing the justification, the IRB will ask, among others, the following questions:

- Is a particular record-based study of "minimal risk" to the subjects?
- How many subjects are in the study and is it possible to locate them so that consent can be requested, obtained, and documented?

Note that cost alone ("it would cost too much") is not considered to be an adequate justification for a consent waiver.

8 Conclusion

Each institution where records reside generally has policies and procedures governing their use by internal staff and by external investigators. Similarly, each state may have laws pertaining to particular kinds of records. For instance, in Washington State, there is a statute outlining under what conditions information contained in medical records may be released and to whom it may be released. Therefore, each investigator conducting records-based research should consult with the Institutional Review Board (IRB) in the state where they are working for information on requirements that apply to the research they are proposing to conduct.

It is recommended that investigators take advantage of IRB review (or other institutional resources or consultations) when designing records-based research and the procedures that can be used to guard privacy and confidentiality. In order to maintain public trust in research, it is important that it is done in a way that provides maximum protections from risks to individuals, while furthering contributions to society's knowledge.

Research Involving Minors

1 Introduction

For as long as people have been doing medical research with human subjects, children have been involved in one context or another. Only recently has either the medical community or society in general raised concerns regarding the rights and welfare of children as subjects in biomedical research.

By the end of this module you will be able to:

- Describe the major historical events that influenced how research with children as subjects is currently conducted.
- Identify problems with research involving children that may violate ethical standards.
- Understand the assent and informed consent requirements on different types of studies involving children.
- Understand the current efforts by the FDA to ensure the inclusion of children in studies on the safety and efficacy of new drugs.

2 Historical Events that have Influenced Research on Children

2.1 Early Medical Experiments

In the 18th century, a number of early "medical experiments" involved the immunization of children. They were deemed good subjects because they had no prior experience with the disease and they were convenient or in close proximity to the investigator. Edward Jenner tested the first smallpox vaccine on his own son, and then on 48 children in an almshouse. The orphans were then infected with smallpox to determine efficacy. Early American pediatrician Benjamin Waterhouse tested an initial shipment of vaccine by vaccinating his own children, then exposing 3 of them to smallpox patients.

The nineteenth century saw growth in a wide range of institutions for children (orphanages, foundling homes, hospitals), reflecting growing public concern for the welfare of children. As these institutions became more common, the health needs of institutionalized children encouraged pediatric experimentation, and these institutions provided ideal conditions for these experiments. Alfred Hess, the medical director of Hebrew Infant Asylum in New York, used his charges to conduct seminal experiments on the anatomy and physiology of digestion, on

pertussis, mumps, and varicella immunizations, and on nutritional deficiencies. He insisted that "conducting experiments in an asylum is ideal because it approximated the conditions insisted on in studying experimental infection in animals but which could rarely be controlled in a study of infection in man."

Some of these experiments were of benefit to the children involved. For example, Louis Pasteur conducted large scale tests of new diphtheria antitoxin in 1893-4 in children in Paris orphanages. Others were less beneficial or dangerous to children. Karl von Ruck tested a “TB vaccine” on 262 children in a Baptist orphanage in North Carolina. Experiments in guinea pigs (performed after the large scale human tests) subsequently showed that the “vaccine” increased the risk of developing TB.

2.2 Growing Concern

The latter half of the 19th century saw the rise of the Anti-vivisection movement. Primarily opposed to use of live animals for medical research, the movements also opposed medical experimentation in charity hospitals, and especially in the use of children as research subjects. The Antivivisectionist press exposed the Rockefeller Institute studies of lutein for the diagnosis of syphilis in 1912. Control subjects for these trials included 46 normal children between 2 and 8 years of age.

Between 1914 and 1920 Alfred Hess and Mildred Fish conducted studies on etiology of scurvy during which they withheld orange juice from institutionalized infants until they developed hemorrhages associated with scurvy. Similar studies performed to determine etiology of rickets. When the details of these studies became public, journalist and social reformer Konrad Bercovici wrote "no devotion to science, no thought of greater good to the greater number, can for an instant justify the experimenting on helpless infants, children pathetically abandoned by fate and entrusted to the community for their safeguarding. Voluntary consent by adults should, of course, be the *sine qua non* of scientific experimentation

2.3 National Research Act (1974)

Research excesses (including research on hepatitis using mentally retarded children at Willowbrook in the 1950s and 1960s) culminating in the exposé of the PHS syphilis experiments, led to the passage of the National Research Act in 1974.

The Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Among the charges of the commission was to "identify the requirements for informed consent to participation in biomedical or behavioral research by children." The Commission report on Research Involving Children was published in 1977, and largely

translated into regulations as 45 CFR 46 (subpart D), "Additional Protections for Children as Research Subjects."

2.4 National Commission Report and Federal Regulations

The National Commission report described a "sliding scale" for research involving children. Research was to be classified according to the risk and the direct benefit to the child. As the risk-benefit relationship of the research became less favorable, additional protections were to be imposed. These categories were translated into sections 45 CFR 46.404, 405, 406 and 407 of subpart D of the DHHS Regulations. Research involving minors must fit into one of these categories to be approvable by the IRB.

See Appendix for summary of National Commission's Analysis of Problematic Issues Involving Children as Research Subjects.

2.5 Assent and Permission in the Federal Regulations

For a child to participate in research, permission of one or both parents is required, and in most cases, assent of the child is also needed. "Assent" means a child's agreement to participate in research. Mere failure to object should not be construed as assent. However, not all children are capable of assent, due to their age, maturity, and psychological state. IRBs are responsible for making the decision when assent is an absolute requirement.

Waiver of consent or assent is also allowed, as per the requirements of 45 CFR 46.116(d). This only applies to studies approvable under 45 CFR 46.404, as will be seen below, since these studies involve no more than minimal risk to the subjects.

3 Categories of Allowable Research

3.1 Research involving no greater than minimal risk (46.404)

To be approvable under 45 CFR 46.404, research must present no more than minimal risk to the subject. Minimal risk is defined as "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or routine medical or psychological examination, of healthy children." Note that minimal risk is weighed against a standard of the life of a healthy child.

3.1.1 Minimal risk procedures might include:

- Venipuncture, bagged urine collection.
- Chest radiograph.
- Psychological tests.
- Classroom observation.

No direct benefit to the child is needed for research to be approvable under 45 CFR 46.404. The permission of one parent and the assent of child are required.

4 Examples of research projects potentially approvable under 46.404 include:

- A study to determine the relationship between maternal age and head circumference at birth. Measurement of head circumference is part of the normal newborn examination, and is therefore minimal risk.

- A study to determine the incidence of asymptomatic proteinuria in school age children. The research involves the analysis of a voided urine collection, which is minimal risk.

4.1 Research involving greater than minimal risk but presenting the prospect of direct benefit (46.405)

Research that presents greater than minimal risk to the subject may be approvable under 45 CFR 46.405 if it holds the potential for direct personal benefit to the child. The benefit must balance or outweigh the risks, and the risk-benefit relationship must be at least as favorable as that seen with standard care. As in the previous section, the permission of one parent and the assent of the child are usually required. However, if the research holds out a prospect of direct benefit to the child which is not available outside the research, the consent of the parent is sufficient; that is, assent of the child, though desirable, is not an absolute requirement.

4.1.1 An example of a research project potentially approvable under 46.405 is:

A pilot study of a shorter duration of antibiotic treatment for uncomplicated otitis media. The potential benefit associated with the shorter duration of treatment is reduced cost, increased compliance, and a reduced rate of antibiotic related diarrhea. The risk associated with the shorter duration of therapy is a higher likelihood of treatment failure.

The risks associated with this research appear to be greater than minimal, but there is the prospect of direct benefit to the child (reduced cost, increased compliance, and a reduced rate of antibiotic related diarrhea). If the IRB decides that the potential benefits balance or outweigh the risks, and the risk-benefit relationship is as favorable as that seen with standard care, this research would be approvable under 46.405.

4.2 Research involving greater than minimal risk and no prospect for direct benefit (46.406)

Research involving greater than minimal risk and no prospect for direct benefit to the subject may be approvable under 45 CFR 46.406. Under this section, the risks associated with the research must satisfy certain specific criteria:

- The risks must be no more than a “minor increase” over minimal risk. No definition of “minor increase is provided in the Federal Regulations. According to the National Commission "…while [minor increase] goes beyond the boundaries of minimal risk, it poses no significant threat to the child’s health or well being." Interventions that might constitute a minor increase include:
    - Catheterized urine collection
    - Skin biopsy or bone marrow biopsy
    - MRI scan with sedation
    - Sensitive survey
- Risks must be commensurate with those inherent in the subject’s actual medical situation. According to the National Commission, "the requirement of commensurability of experience should assist children who can assent to make a knowledgeable decision about their participation in research, based on some familiarity with the procedure and it’s effects.. "
- The research must be likely to yield knowledge of vital importance about the child’s disease or condition.

To participate, the permission of both parents and the assent of the child are required.

4.2.1 An example of a research project potentially approvable under 46.406 is:

A study to determine the clinical relevance of a new technique to quantitate minimal residual disease (MRD) during therapy for acute lymphoblastic leukemia in children. The study requires one additional bone marrow aspirate be performed during the course of treatment. Therapy for the subject will not be altered based on the results of the assay. However, if it can be shown that the presence of MRD predicts poor outcome, in the future, patients with MRD can receive more intensive treatment and increase their chance of cure.

It can be argued that the risk of a bone marrow aspirate in a normal child is only a minor increase over minimal risk. Further, the risk appears commensurate with risks inherent in the subject’s actual medical situation, and the research may yield knowledge of vital importance about the child’s disease (leukemia). Therefore, this research may be approvable under 46.406.

4.3 Research otherwise not approvable (46.407)

Research not approvable under any of the previous sections, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare of children, may still be approvable. The research must be reviewed by a panel of experts appointed by the Secretary of DHHS. The research must be conducted in accordance with sound ethical principles. The assent of subjects and permission of parents must be obtained.

4.4 Inclusions of Wards (e.g., Foster Children)

Remembering the exploitation of orphans as subjects of medical research, the National Commission also specifically addressed the inclusion of wards of the state. They noted that it is important to "learn about the effects of the settings in which children who are wards of the state may be placed … in order to improve the care that is provided for such children." Further, they thought it important to avoid embarrassing these children by excluding them from research in which their peers in a school, camp or other group setting might be participating. To these ends, the commission notes that the IRB should "evaluate the reasons for including wards of the state as research subjects and assure that such children are not the sole participants in a research project unless the research is related to their status as orphans, abandoned children, and the like."

45 CFR 46.409, reflecting the National Commission report, restricts the involvement of wards in research that is greater than minimal risk and without direct subject benefit (research approvable under 46.406). Wards may only be enrolled in such research if the research is related to their status as wards, or is conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. Further, the regulations require that each child have an advocate appointed who has the background and experience to act in, and agrees to act in, the best interests of the child, and who is not associated in any way with the research, the investigators, or the guardian organization. It is important to note that the IRB has the responsibility to appoint the guardian and not the investigator.

5 Other Guidelines on the Inclusion of Children in Research Involving Human Subjects

5.1 NIH Guidelines

Although the adoption of subpart D marked a high point in the protection of children, there were concerns that children would also be denied the potential benefits of medical research. In 1977 the American Academy of Pediatrics agreed that children capable of providing assent have the right to refuse research participation. However, the Academy also pointed out that exclusion of children

from drug studies was more unethical than clinical testing, and could lead to devastating results.

The antibiotic chloramphenicol was released in the 1950s without adequate testing in infants and children. As use of the drug became more common, reports of a serious and often fatal reaction called the Grey Baby Syndrome surfaced. This reaction was related to slow clearance of the drug in infants as compared to adults, due to deficiency in hepatic glucuronyl transferase in infants. Similarly, though less devastating, widespread use of tetracycline in children was subsequently shown to be associated with dental dysplasia.

Nonetheless, children continued to be excluded from drug testing. A survey of the 1991 Physician's Desk Reference showed that 81% of listed drugs contained language disclaiming use in children or restricting use to certain age groups.

In March 1998, the NIH published Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects, to answer some of these concerns. The guidelines state "... children must be included in all human subjects research conducted or supported by the NIH unless there are scientific or ethical reasons not to include them". Possible justifications for the exclusion of children from NIH Funded studies include:

- The research topic is irrelevant to children.
- Knowledge sought is already available in children or will be obtained from another ongoing study.
- A separate age-specific study is warranted and preferable, or
- Insufficient data are available in adults to determine potential risks in children.

In addition, the NIH Guidelines state that "inclusion of children must be in compliance with all applicable subparts of 45 CFR 46"

For more details see NIH Policy and Guidelines on the Inclusion of Children as Participant in Research involving Human Subjects

5.2 FDA Guidance and Regulation

In 2001, in response to the Children's Health Act of 2000, the FDA adopted Additional Protections for Children in Clinical Investigations (21 CFR 50 subpart D). These regulations are largely equivalent to the HHS regulations at 45 CFR 46 subpart D.

The FDA has also attempted to answer concerns regarding the exclusion of children, by taking a “carrot and stick” approach. The Best Pharmaceuticals for Children Act (2002) extends marketing exclusivity for pharmaceutical companies

who test new drugs in children. The Pediatric Research Equity Act (2004) enables FDA to require testing of drugs for pediatric use.

6 Summary

Early medical experiments involving children, especially institutionalized children, lacked sound ethical research practices. Growing public concern over the exploitation of children led to movements aimed at protecting the rights of children and resulted in the establishment of ethical standards and federal regulation. The National Research Act for the Protection of Human Subjects in Biomedical and Behavioral Research established the National Commission. The National Commission Report provides a “sliding scale” classifying research according to the risk and the direct benefit to the child, and provides the requirements for assent and informed consent for participation in research involving children. Specific requirements are:

6.1 Research involving no greater than minimal risk (46.404) requires the permission of one parent and the assent of the child

6.2 Research involving greater than minimal risk but presenting the prospect of direct benefit (46.405) requires:

- The benefit must balance or outweigh the risks.
- The risk-benefit relationship must be at least as favorable as that seen with standard care.
- Permission of one parent.
- Assent of the child, unless the research holds out a prospect of direct benefit to the child which is not available outside the research.

6.3 Research involving greater than minimal risk and no prospect for direct benefit (46.406) requires:

- The risk is only a minor increase over minimal risk.
- The risks are commensurate.
- The research will likely yield knowledge of vital importance.
- Permission of both parents.
- Assent of the child.