

**The primary objectives of this course are to increase knowledge among investigators and key personnel regarding research ethics and to protect human subjects involved in research studies at Indiana University and Clarian Health Partners.**

## 1. BRIEF HISTORY OF RESEARCH ETHICS

Prior to 1906, when the Pure Food and Drug Act was passed, there were no regulations regarding the ethical use of human subjects in research. There were no consumer regulations, no Food and Drug Administration (FDA), no Common Rule, and no Institutional Review Board (IRB). What follows is a brief discussion of why federal rules and regulations were established and why the IRB became a necessity.

**Nuremberg Code.** The most dramatic and well-known chapter in the history of research with human subjects opened on December 9, 1946, when an American military tribunal opened criminal proceedings against 23 leading German physicians and administrators for their willing participation in war crimes and crimes against humanity. Among the charges were that German physicians conducted medical experiments on thousands of concentration camp prisoners without their consent. Most of the subjects of these experiments died or were permanently crippled as a result.

As a direct result of the trial, the [Nuremberg Code](#) was established in 1948, stating that “The voluntary consent of the human subject is absolutely essential,” making it clear that subjects should give consent and that the benefits of research must outweigh the risks.

Although it did not carry the force of law, the Nuremberg Code was the first international document which advocated voluntary participation and informed consent.

**Thalidomide.** In the late 1950s, thalidomide was approved as a sedative in Europe; it was *not* approved in the United States by the FDA. The drug was prescribed to control sleep and nausea throughout pregnancy, but it was soon found that taking this drug during pregnancy caused severe deformities in the fetus. Many patients did not know they were taking a drug that was not approved for use by the FDA, nor did they give informed consent. [Some 12,000 babies were born with severe deformities due to thalidomide.](#)

U.S. Senate hearings followed and in 1962 the so-called “[Kefauver Amendments](#)” to the Food, Drug and Cosmetic Act were passed into law to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to FDA the effectiveness of their products before marketing them.

**Declaration of Helsinki.** In 1964, the World Medical Association established recommendations guiding medical doctors in biomedical research involving human subjects. The Declaration governs international research ethics and defines rules for “research combined with clinical care” and “non-therapeutic research.” The [Declaration of Helsinki](#) was revised in 1975, 1983, 1989 and 1996 and is the basis for Good Clinical Practices used today.

Issues addressed in the Declaration of Helsinki include:

- Research with humans should be based on the results from laboratory and animal experimentation

- Research protocols should be reviewed by an independent committee prior to initiation
- Informed consent from research participants is necessary
- Research should be conducted by medically/scientifically qualified individuals
- Risks should not exceed benefits

**Tuskegee Syphilis Study (1932-1972).** During a research project conducted by the U.S. Public Health Service, 600 low-income African-American males, 400 of whom were infected with syphilis, were monitored for 40 years. Free medical examinations were given; however, subjects were not told about their disease. Even though a proven cure (penicillin) became available in the 1950s, the study continued until 1972 with participants being denied treatment. In some cases, when subjects were diagnosed as having syphilis by other physicians, researchers intervened to prevent treatment. Many subjects died of syphilis during the study. The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare only after its existence was publicized and it became a political embarrassment. In 1997, under [mounting pressure](#), President Clinton [apologized](#) to the study subjects and their families.

**National Research Act (1974).** Due to the publicity from the Tuskegee Syphilis Study, the National Research Act of 1974 was passed. The National Research Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was charged to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles.

The Commission drafted the Belmont Report, a foundational document in for the ethics of human subjects research in the United States.

**Take Home Points:**

- Nazi atrocities in World War II drew attention to the lack of international standards on research with human subjects and led to the formulation of the [Nuremberg Code](#).
- The [thalidomide disaster](#) led to the adoption of the “[Kefauver Amendments](#)” to the Food, Drug and Cosmetic Act, requiring drug manufacturers to prove to the FDA the effectiveness of their products before marketing them.
- The [Declaration of Helsinki](#) is the basis for Good Clinical Practices used today.
- The Tuskegee Syphilis Study is probably the worst case of unethical human subjects research in the history of the United States.
- The National Research Act codified the requirement that human subjects in research must be protected and set the stage for the issuance of the Belmont Report.

## 1.1 THE BELMONT REPORT

Carrying out its charge, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research prepared the Belmont Report in 1979. The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. The Report is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. The three basic ethical principles and their corresponding applications are:

<b>Principle</b>	<b>Application</b>
<p><b>Respect for persons</b></p> <ul style="list-style-type: none"> <li>• Individuals should be treated as autonomous agents</li> <li>• Persons with diminished autonomy are entitled to protection.</li> </ul>	<p><b>Informed consent</b></p> <ul style="list-style-type: none"> <li>• Subjects, to the degree that they are capable, must be given the opportunity to choose what shall or shall not happen to them</li> <li>• The consent process must include three elements: <ul style="list-style-type: none"> <li>○ information,</li> <li>○ comprehension, and</li> <li>○ voluntary participation</li> </ul> </li> </ul>
<p><b>Beneficence</b></p> <ul style="list-style-type: none"> <li>• Human subjects should not be harmed</li> <li>• Research should maximize possible benefits and minimize possible harms.</li> </ul>	<p><b>Assessment of risks and benefits</b></p> <ul style="list-style-type: none"> <li>• The nature and scope of risks and benefits must be assessed in a systematic manner</li> </ul>
<p><b>Justice</b></p> <ul style="list-style-type: none"> <li>• The benefits and risks of research must be distributed fairly.</li> </ul>	<p><b>Selection of subjects</b></p> <ul style="list-style-type: none"> <li>• There must be fair procedures and outcomes in the selection of research subjects</li> </ul>

### Take Home Point:

The Belmont Report established three basic ethical principles – **autonomy/respect for persons, beneficence and justice** – which are the cornerstone for regulations involving human subjects.

### Related Internet Link:

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm> - xethical

## 2. CURRENT REGULATIONS

In 1981, the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) issued regulations based on the Belmont Report. DHHS issued Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of human subjects). The FDA issued CFR Title 21 (food and drugs), Parts 50 (protection of human subjects) and 56 (Institutional Review Boards).

In 1991, the core DHHS regulations (45 CFR Part 46, Subpart A) were formally adopted by more than a dozen other Departments and Agencies that conduct or fund research involving human subjects as the Federal Policy for the Protection of Human Subjects. This widely accepted policy is now referred to as the "Common Rule." Today, the 1991 Federal Policy is shared by 17 Departments and Agencies, representing most, but not all, of the federal Departments and Agencies sponsoring human-subjects research.

The **main elements of the Common Rule** include:

- requirements for assuring compliance by research institutions;
- requirements for researchers obtaining and documenting informed consent;
- requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping.
- additional protections for certain vulnerable research subjects-- pregnant women, prisoners, and children

In addition, certain federally sponsored and much privately sponsored research is subject to the regulations of the Food and Drug Administration (FDA) at 21 CFR Parts 50 and 56. FDA regulations confer protections on human subjects in research when a drug, device, biologic, food additive, color additive, electronic product, or other test article subject to FDA regulation is involved. FDA regulations and the provisions of the Common Rule are largely congruent, although some significant differences exist.

### **Take Home Point:**

Both the Common Rule and the FDA regulations provide protections for human subjects in research and mandate IRB oversight of such research.

### **Related Internet Links:**

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

<http://www.fda.gov/cdrh/manual/appendb.html>

<http://www.fda.gov/cdrh/manual/appendc.html>

## 2.1 MULTIPLE PROJECT ASSURANCE

Within DHHS, the Office for Human Research Protections (OHRP) oversees implementation of the human-subject regulations in all DHHS facilities as well as domestic and foreign institutions or sites receiving DHHS funds. In keeping with the provisions of the Common Rule, OHRP requires that each DHHS agency and research institution that conducts research involving human subjects sets forth the procedures it will use to protect human subjects in a policy statement called an "Assurance" of compliance. Under the Common Rule, OHRP has authority for approving an Assurance at DHHS-funded institutions for federal-wide use.

At OHRP's discretion, institutions with a large volume of research and demonstrated expertise in human subjects protection may be granted a Multiple Project Assurance (MPA). A Multiple Project Assurance, as the term implies, is an institution's pledge of full human subject protections for multiple projects at the institution. Indiana University and Clarian Health Partners hold such an Assurance. This assurance identifies our responsibilities and explains the steps that we will take to meet the federal regulations for research on human subjects. The Assurance requires that *all* research projects involving human subjects, regardless of funding source, conducted by an employee of Indiana University or Clarian Health Partners be reviewed and approved by an Institutional Review Board (IRB) *prior* to initiating any research. Failure by any investigator to adhere to the provisions of the Assurance may cause the institution to have this Assurance suspended or revoked. Therefore, it is important that all investigators be knowledgeable about the contents of the MPA.

**A copy of the University/Clarian Health Partners' Assurance may be obtained at:**

<http://www.iupui.edu/%7Eeresgrad/spon/assurance.htm>

**Take Home Point:**

Indiana University and Clarian Health Partners, through the MPA, have pledged to protect human subjects and comply with all relevant federal regulations with respect to all research, whether funded or unfunded.

**Related Internet Links:**

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/as-types.htm>

## 2.2 WHAT IS RESEARCH?

### Definition:

**Research** is defined by the Department of Health and Human Services as “*a systematic investigation, including research development testing and evaluation, designed to develop or contribute to generalizable knowledge*” (45 CFR 46).

### Examples:

Such studies may involve various invasive or non-invasive procedures, removal of body tissues or fluids, administration of drugs, exposure to various forms of radiation, alteration of diet or environment, interviews, surveys, simple observation, administration of questionnaires, or review of records.

- A good rule of thumb for determining whether or not a particular project qualifies as research is to consider whether or not the results will be published or presented in some form or forum outside of the institution. For example, is the project being undertaken with the notion that a paper or journal article may be published or that a poster or paper may be presented at a conference or community gathering? If so, the project most likely will qualify as research and thus is subject to review by the Institutional Review Board (IRB).

**When in doubt, contact the IRB Staff to help determine whether a particular project is “research” as defined by the institution and federal regulations!**

### TAKE HOME POINT:

- If you are planning to publish the results of a project, it is almost always regarded as “research.” Research can involve a variety of methods and materials. If you are unsure about your project, check with IRB Staff.

### Related Internet Links:

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>  
[http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter1.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter1.htm)

## 2.3 WHAT IS A HUMAN SUBJECT?

### Definition:

A **Human Subject** is defined 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.*

*Interventions* may be:

- *physical procedures by which data are gathered*  
OR
- *manipulations of the subject or the subject's environment that are performed for research purposes.*

IRBs review research that involves human subjects.

### Examples:

- an individual involved in a clinical trial
- an individual involved in a psychological experiment
- an individual involved in a group that is being studied
- an individual involved in a drug study
- an individual asked to fill out a survey or questionnaire

NOTE: Because a human subject is defined as a “living individual,” tissues taken from an autopsy and then studied may not require IRB review.

### TAKE HOME POINT:

- A human subject is any individual about whom an investigator obtains data through intervention or interaction or identifiable private information. If you are unsure as to whether or not your study involves human subjects, contact the IRB staff for further clarification.

### Related Internet Links:

IUPUI	<a href="http://www.iupui.edu/%7Eeresgrad/spon/rescomcontent2.htm">http://www.iupui.edu/%7Eeresgrad/spon/rescomcontent2.htm</a>
IUB	<a href="http://www.indiana.edu/~resrisk/hmpg.html">http://www.indiana.edu/~resrisk/hmpg.html</a>

## 2.4 WHAT IS STUDENT RESEARCH AT IU?

### Definition:

Remember that research is defined in the Federal Regulations as “a systematic investigation designed to develop or contribute to generalizable knowledge.” Since classroom assignments typically are neither intended to, nor likely to lead to generalizable results, the IRB does not normally include these projects under its operational definition of research, unless the student and/or instructor plans to present and/or publish that work outside of the bounds of the institution.

*HOWEVER*, regardless of whether any student research is conducted as part of a course assignment or not, student research projects that

- may place subjects at risk  
OR
- are undertaken with the intent of adding to generalizable knowledge  
OR
- involve special populations including pregnant women, fetuses, prisoners, minors, or human in vitro fertilization (considered vulnerable research subjects)

*are subject to IRB review.*

Subjects are considered to be at “risk” if the procedures used and/or the questions asked do not fall under what is construed as being ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Instructors are responsible for screening individual research projects and making an initial determination as to whether the project may fall in the category of research. If an instructor determines that a student project is characterized by one of the above criteria, appropriate forms must be provided to the IRB for its review and approval prior to initiating the research. IRB Staff can be contacted to obtain proper forms.

**Examples:** Classroom or independent study projects  
Theses  
Dissertations

### TAKE HOME POINT:

- **Any** student research project that places subjects at risk, is undertaken to contribute to generalizable knowledge, or involves special populations is subject to IRB review and approval.

### Related Internet Links:

IUPUI	<a href="http://www.iupui.edu/%7Eeresgrad/spon/rescomcontent2.htm">http://www.iupui.edu/%7Eeresgrad/spon/rescomcontent2.htm</a>
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Human Subjects Course

<b>IUB</b>	<a href="http://www.indiana.edu/~resrisk/stures.html">http://www.indiana.edu/~resrisk/stures.html</a> <a href="http://www.indiana.edu/~resrisk/sturespo.html">http://www.indiana.edu/~resrisk/sturespo.html</a>
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### **3. WHAT IS AN INSTITUTIONAL REVIEW BOARD (IRB)?**

According to federal regulations, an Institutional Review Board (IRB) is an administrative body established to protect the rights and welfare of human research participants recruited to participate in research activities that are conducted under the auspices of the institution with which it is affiliated. An IRB has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction as specified by both federal regulations and local institutional policy.

IRBs have other responsibilities, too. For example, IRBs assess suspected or alleged protocol violations, subject complaints, or violations of external regulations or institutional policies. IRBs also conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once a year, and IRBs assess proposed changes in research activities or plans.

#### **TAKE HOME POINT:**

- Essentially, an IRB works to review research and ensure that human subjects are protected against undue or unnecessary invasion of privacy, disregard for human dignity, and physical, psychological, or social harm.

Related Internet Link: [http://ohrp.osoph.dhhs.gov/irb/irb\\_guidebook.htm](http://ohrp.osoph.dhhs.gov/irb/irb_guidebook.htm)

### 3.1 IRB COMPOSITION REQUIREMENTS

Members of an IRB will consist of at least five (5) members and will include a diversity of membership as outlined in the Multiple Project Assurance (MPA) and federal requirements.

IUPUI	The Chancellor or the Chancellor's designee of IUPUI appoints regular and alternate members. The term of membership is two years, beginning July 1 and ending June 30. Members may be reappointed for an unlimited number of terms.
IUB	The Vice President for Research appoints regular and alternate members for terms of two years, beginning September 1 and ending August 30. Members may be reappointed for an unlimited number terms.

IRB members must have varying backgrounds to promote complete and adequate review of research. In addition, members must be sufficiently qualified through experience and expertise to include considerations of gender, racial and cultural heritage, and sensitivity to issues such as community attitudes. IRB membership includes individuals who are knowledgeable about and experienced in working with vulnerable categories of subjects, including children, prisoners, pregnant women, or handicapped or mentally disabled persons. Finally, IRBs also include at least one member whose primary concerns are in non-scientific areas and at least one member who is not otherwise affiliated with the institution.

#### TAKE HOME POINT:

IRBs are composed of members with varying backgrounds, expertise, and experience. A diverse representation functions to promote complete and adequate review of research.

**Related Internet Link:** [http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter1.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter1.htm)

## 3.2 IRBs AT IUPUI AND HOW TO CONTACT THEM

IUPUI has four IRBs, each of which are qualified and established to review the type of research submitted to it. Although investigators typically designate a particular board in which to submit their research, IRB staff may need to route research submissions to the board that has the expertise to review various specialized areas of research or route to another IRB due to workload considerations of a particular board.

### **IRB-01 Behavioral/Social Sciences Board:**

*Reviews behavioral/social sciences research for IUPUI and Clarian investigators.*

### **IRB-02 IUPUI Medical:**

*Reviews IUPUI biomedical research; includes expertise in the area of oncology (adult), nephrology, infectious disease, dentistry, clinical pharmacology, dermatology, psychiatry, and endocrinology.*

### **IRB-03 Clarian at Methodist Hospital campus:**

*Primarily reviews biomedical research conducted at the Methodist Hospital campus or is collaborative research between Clarian investigators.*

### **IRB-04 IUPUI Medical:**

*Reviews IUPUI biomedical research; includes expertise in the areas of infectious disease, pediatrics, nephrology, radiology, oncology (adult and pediatric), neurology, cardiology, ophthalmology, and surgery.*

Each board meets once a month and deadlines are pre-established and strictly adhered to for submission of materials for each meeting. Refer to the IRB Instruction Packet at <http://www.iupui.edu/%7Eeresgrad/spon/irbpack.rtf> for more information about specific deadlines and meeting dates.

Please contact the IRB staff if you have any questions about these policies at:

Research and Sponsored Programs  
Union Building, Room 618  
620 Union Dr.  
Indianapolis, IN 46202  
(317) 274-8289  
[resrisk@iupui.edu](mailto:resrisk@iupui.edu)

### **TAKE HOME POINT:**

- IUPUI has four IRBs that are organized by subject area and expertise. Research projects involving human subjects must be submitted to one of these local boards to obtain appropriate approvals.

**Related Internet Link:** <http://www.iupui.edu/%7Eeresgrad/spon/rescomcontent2.htm>

### **3.3 THE IRB AT IUB AND HOW TO CONTACT IT**

IUB has one IRB, the Committee for the Protection of Human Subjects, or Human Subjects Committee (HSC).

Exempt and expedited level projects are reviewed weekly by the chair of the HSC, currently on Wednesdays. Applications must be received by 5:00 p.m. on Friday in order to be reviewed the following week.

The Committee meets monthly to review those projects requiring full review, normally on the third Thursday of each month. Applications must be received by 5:00 p.m. on the Friday four weeks before the month's meeting in order to be reviewed that month. There are some exceptions to these schedules and researchers are urged to contact the Committee's office, 855-3067, for the current schedule. Investigators should allow sufficient time for review prior to the beginning date of the project. While projects are reviewed frequently, the entire process can take up to three weeks. Projects that require full Committee review may take longer.

Please contact the HSC staff if you have any questions about these policies at:

Human Subjects Committee  
Office of Research Compliance  
Carmichael L03  
503 East Kirkwood Avenue  
Bloomington IN 47405  
(812) 855-3067  
[iub\\_hsc@indiana.edu](mailto:iub_hsc@indiana.edu)

#### **TAKE HOME POINT:**

- Research projects on the Bloomington campus involving human subjects must be submitted to the HSC to obtain approval.

**Related Internet Link:** <http://www.research.indiana.edu/rschcomp/operate.html>

### 3.4 EXEMPT STUDIES

Research projects are reviewed at one of three levels, depending on the level of risk to the human subjects and on the federal regulations that define the categories of review, which are:

- exemption from full IRB review,
- expedited IRB review, and
- full IRB review.

Our MPA states:

“Research investigators who intend to involve human research subjects will not make the final determination of exemption from applicable Federal regulations or provisions of this Assurance.”

Therefore, the level of review cannot be determined by the investigator.

Investigators also do not have the authority to determine whether research involving human subjects is exempt from full review. Researchers must file an application requesting that a project be classified as exempt. If the project does not qualify as exempt, it is referred back to the investigator with the appropriate application forms. Types of research which may fit into exempt categories include:

- Research on instructional strategies conducted in established or commonly accepted educational settings;
- Research, except research involving minors, involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior;
- Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available, or if the information is recorded by the investigator in such a manner that subjects cannot be identified;
- Research and demonstration projects, which are conducted by or subject to the approval of department or agency heads; and
- Taste and food quality evaluation and consumer acceptance studies,
  - (i) if wholesome foods without additives, or
  - (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration, or

approved by the Environmental Protection Agency, or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

For additional information and to submit an application, please go to:

IUPUI: <http://www.iupui.edu/~resgrad/spon/download.htm>.

IUB: <http://www.indiana.edu/~resrisk/forms.pdf>

**Take Home Point:**

Even if an investigator believes that a project is exempt, an application must be submitted to the IRB Office for a final determination.

**Related Internet Link:**

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm> - 46.101

### 3.5 EXPEDITED STUDIES

Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. Activities approved in the federal regulations include:

1. Collection of hair and nail samples;
2. Collection of excreta and external secretions;
3. Recording of data from subject 18 years of age or older using noninvasive procedures;
4. Collection of blood samples in minimal amounts;
5. Collection of dental plaque and calculus;
6. Voice recording;
7. Moderate exercise by health volunteers;
8. Study of existing data;
9. Research on an individual or group behavior that involves no manipulation of the subjects and is not stressful; and
10. Certain kinds of research on drugs and devices.

**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.

**Expedited review** means that the research is considered “minimal risk” and does not require full IRB review. The expedited subcommittee, including members of the IRB, reviews and approves the research.

For additional information and to submit an application, please go to

IUPUI: <http://www.iupui.edu/~resgrad/spon/download.htm>.

IUB: <http://www.indiana.edu/~resrisk/forms.pdf>

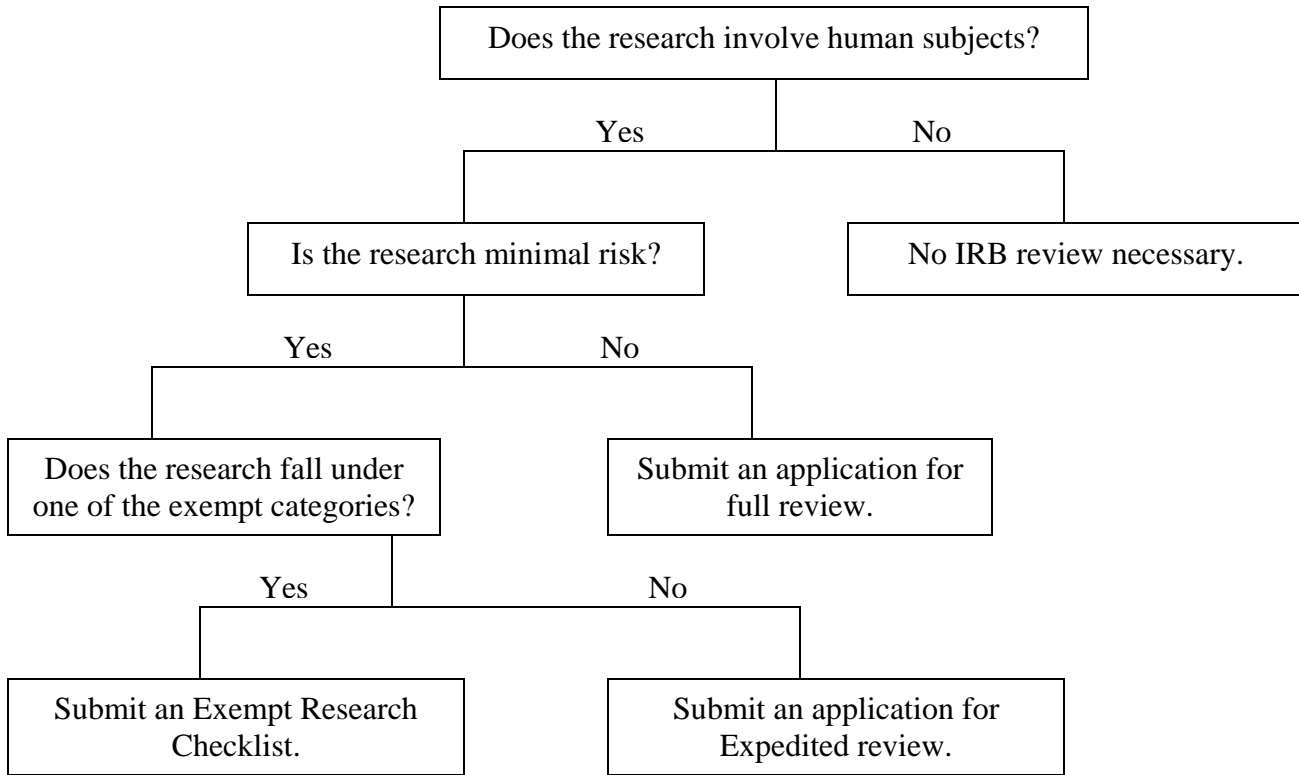
#### **TAKE HOME POINT:**

If your research is considered “minimal risk” as defined in this section, it could qualify for the expedited review process and is not required to be reviewed at a meeting of the full IRB board.

#### **RELATED INTERNET LINK:**

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm>

### 3.6 Research Decision Tree



### **3.7 FULL REVIEW BY THE IRB**

Research that involves greater than minimal risk requires review and approval by a full IRB board composed of members qualified to review research in that field. Risks to research subjects posed by participation in research should be justified by the anticipated benefits to the subjects or society. Research that requires full Board review includes but is not limited to:

- Certain types of research involving children, pregnant women, fetuses and other vulnerable populations;
- Research involving prisoners
- Research that involves experimental drugs or devices;
- Research that involves most invasive procedures;
- Survey research that involves sensitive questions or is likely to be stressful for the subject.

For additional information and to submit an application, please go to:

<http://www.iupui.edu/~resgrad/spon/download.htm>.

#### **TAKE HOME POINT:**

If any of the above-mentioned types of research is being proposed, review and approval is required by a full IRB Board.

### 3.8 THE IRB REVIEW PROCESS

Research projects should be reviewed in a manner so as to provide for the protection of the subject against undue or unnecessary invasion of privacy, disregard for human dignity, and physical, psychological or social harm. In most cases, this will involve approval of a consent form written in a language that is understandable to the research subject or representative (usually at the eighth-grade reading level). The consent must provide sufficient information so that the subject is fully informed of the risks and benefits that might be reasonably expected.

IRB review assures that:

- risks to subjects are minimized;
- risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result;
- selection of subjects is equitable;
- there is proper informed consent and documentation of informed consent;
- when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and
- additional safeguards have been included in the study to protect the rights and welfare of any subjects likely to be vulnerable to coercion or undue influence

Once research is initiated, IRBs have continuing responsibilities. These include:

- The conduct of continuing review at intervals appropriate to the degree of risk, and in any event, not less than once per year.
- Authority to observe or have a third party observe the consent process and the research.
- Receipt of prompt reports from investigators of any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the IRB`s requirements or determination, or with the regulations.
- Authority to suspend or terminate IRB approval of research that is not being conducted in accord with the IRB`s requirements or that has been associated with unexpected serious harm to subjects.

**TAKE HOME POINT:**

The IRB has many responsibilities to protect human subjects while conducting its review before the research is initiated and after it has begun.

**RELATED INTERNET LINK:**

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm> - 46.111

### **3.9 IRB ACTIONS**

When a study is reviewed at a full meeting of the IRB Board, there are four possible actions that can be taken:

- Final approval - There are no changes needed in the study and the investigator can proceed with the research without further delay;
- Provisional approval - There are minor revisions that need to be made, but full review is not required by the IRB. After the revisions are completed, the study can be reviewed and signed by the Chair or Board member giving final approval;
- Tabled - There are major problems or concerns with the study that impact the protection of the human subjects to be involved, and the study must be reviewed again by the IRB at a subsequent meeting after the investigator has addressed all the reviewers' concerns;
- Disapproved - Specific reasons for disapproving research will be communicated to the investigator. The study may not be resubmitted unless completely revised.

#### **TAKE HOME POINT:**

Actions that the IRB will take on a study depend upon how adequately the subjects will be protected as listed in the proposed study. Extensive changes may be necessary.

#### **RELATED INTERNET LINK:**

<http://www.iupui.edu/%7Eeresgrad/spon/irbpoly.pdf>

## 4. THE INFORMED CONSENT STATEMENT

### Basic (Required) Elements

The informed consent is one of the primary ethical requirements supporting research with human subjects; it reflects the basic principle of *respect for persons*. Informed consent is an ongoing process and assures that prospective human subjects will understand the nature of the research in which they may participate and can *knowledgeably* and *voluntarily* decide whether or not to participate. This assurance protects all parties involved – both the subject, whose autonomy is respected, and the investigator, who otherwise may face legal hazards.

The federal regulations require that certain information **MUST** be provided to prospective research participants. Basic requirements are listed below.

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which may be experimental
- A description of any risks and benefits, including a statement as to whether or not subjects will be compensated for their participation and any specific terms of compensation
- A discussion of alternative procedures or courses of treatment, if any
- A statement outlining the extent to which confidentiality of records identifying the subject will be maintained
- A statement that explains whether there are any costs to the subject for taking part in the study and additionally explains whether medical treatment or compensation is available if injury occurs, and if so, whether the costs of such treatment are to be the subject's responsibility and where further information can be obtained
- An explanation of whom to contact for answers to questions about the research and report any study-related problems (the investigator's name and telephone number)
- A statement regarding subjects' rights or patient representatives (including appropriate phone numbers)

The informed consent statement **MUST** be written in a language that is understandable to the subject population. IU recommends informed consent statements be written in **8<sup>th</sup> grade language**.

Finally, the informed consent **MAY NOT** contain any exculpatory language. In other words, subjects may not be asked to waive (or appear to waive) any of their legal rights, nor may they be asked to release the investigator, sponsor, or institution (or its agents) from liability from negligence.

**TAKE HOME POINT:**

The informed consent statement is an important and necessary method of communication between an investigator and a potential research participant. Several elements must be addressed in a consent. The consent must be written in language that is understandable to the subject population, should include what facts a subject might want to know before deciding whether or not to participate in the research, and should not contain any exculpatory language.

A sample consent and consent requirement checklist is available at:

<http://www.iupui.edu/%7Eresgrad/spon/irbpack.rtf>

**Related Internet Link:** [http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter3.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter3.htm)  
<http://www.iupui.edu/~resgrad/>  
<http://www.indiana.edu/~resrisk/informed.html>

## 4.1 THE INFORMED CONSENT STATEMENT

### Additional Content in Certain Circumstances

Depending upon what kind of treatments or procedures may be involved in a particular research project, there may be additional items that must be addressed in an informed consent statement. Where appropriate, these items include:

- A statement that the particular treatment or procedure may involve risks to the subject that are currently unforeseeable
- A description outlining anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
- An explanation of any additional costs to the subject that may result from participation in the research
- A statement discussing the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A description suggesting that significant new findings developed during the course of the research which may relate to the subject's willingness to participate will be provided to the subject
- A statement including the approximate number of subjects involved in the study

### TAKE HOME POINT

Carefully consider what your research project entails and ensure that if any additional items are necessary they are included in the informed consent statement.

**Related Internet Link:** [http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter3.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter3.htm)

## 4.2 THE PROCESS OF INFORMED CONSENT

Since the central requirement for human subjects research is that people participate voluntarily, the consent process is one of the most important parts of a research project. The process must assure that the potential subject understands the study and its risks and benefits and can certify his or her willingness to participate.

In spite of the common term, it may be best for investigators to think of the process as one of informed **choice**. The task is not to *obtain consent*, but to *ensure that prospective subjects are able to make a free and informed choice to participate or decline to participate in the study*.

Investigators should think of informed consent not as a form that must be signed, but as an **educational process** that takes place between the investigator and the prospective subject. Because obtaining informed consent is an educational process, the investigator should do what he or she can to enhance the prospective subject's comprehension of the information presented. The nature of the proposed subject population, the type of information to be conveyed, and the circumstances under which the consent process will take place (e.g., manner, timing, place, personnel involved) should all be considered.

Consent is also an **ongoing** educational process. It starts well before any forms are signed and continues until the subject's participation is complete. The informed consent process involves:

- meeting with a potential subject,
- finding out whether he or she is capable of giving consent on an ongoing basis, and
- discussing the purpose, risks, and benefits of participation, including any risks that are discovered **after** the informed consent document is first signed.

The burden of ensuring that someone who might participate genuinely understands and continues to understand the research falls upon the researcher, not upon the prospective subject.

The consent form itself formalizes the agreement to participate and should be designed to document the process.

### TAKE HOME POINT:

The informed consent document is only a part of the informed consent process. The process should be seen as an ongoing one which assures that subjects are fully informed and able to provide consent.

### Related Internet Link:

[http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter3.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter3.htm) - e2

### 4.3 WAIVING OR MODIFYING INFORMED CONSENT

The federal regulations for human subjects research allow a waiver of the requirement for informed consent in some instances. An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

- the research involves no more than minimal risk to the subjects;

(Note: Loss of confidentiality is, under most circumstances, more than minimal risk. However, contact by primary caregivers or others who by the nature of their involvement with the subject already have access to the data, will be considered as no further loss of confidentiality and, therefore, may be less of a risk to subject confidentiality. Risk may also vary with the type of information being collected).

- the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- the research could not practicably be carried out without the waiver or alteration; and
- whenever appropriate, the subjects will be provided with additional pertinent information after participation.

A waiver or alteration of the informed consent is also possible if the purpose of the research is to study some types of public service programs. Only the IRB can waive or alter the consent process. Investigators may not make this decision.

These provisions for waiver do not apply to FDA regulated research. The FDA allows a waiver of informed consent only under emergency conditions.

#### **Take Home Point:**

The IRB can waive or alter the informed consent process in certain limited circumstances. The investigator is not authorized to make this decision without IRB approval.

#### **Related Internet Link:**

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm> - 46.116

#### 4.4 WAIVER OF WRITTEN INFORMED CONSENT

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

- 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. Each subject will be asked whether they want documentation linking them with the research. The subject's wishes will govern.

**OR**

- 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.

The IRB may require the investigator to provide subjects with a written statement regarding the research.

#### **Take Home Point:**

A waiver of written consent may be granted in limited circumstances. The investigator is not authorized to make this decision without IRB approval.

#### **Related Internet Link:**

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm> - 46.117

## 4.5 EMERGENCY WAIVER OF INFORMED CONSENT

On October 2, 1996, the FDA and NIH published changes in the regulations concerning the waiver of informed consent requirements in emergency research protocols. In very rare instances and under special emergent circumstances, the requirement for obtaining informed consent may be waived. Waiver of consent is limited to those studies involving subjects in life-threatening circumstances and who cannot give informed consent. Since such studies would likely involve a higher degree of risk than research not involving emergency procedures, protocols on which waivers have been approved may be reviewed by the IRB more frequently.

Special requirements exist which must be fulfilled before the IRB can finally approve a study involving an emergency waiver of informed consent. The regulations outline **specific** requirements that must be met by both the IRB and an investigator who will conduct research "in emergent circumstances." An exception from informed consent requirements for emergency research may be sought **ONLY** for research to be conducted under which all of the following conditions prevail:

- prospective subjects are in a life-threatening situation;
- available treatments are unproven or unsatisfactory;
- research is necessary to determine what intervention is best;
- informed consent is not feasible because
  - the patient cannot consent due to the medical condition,
  - intervention must be made before consent from a patient's representative is feasible, and
  - consent cannot be obtained in advance because prospective subjects cannot reliably be identified ahead of time; and
- risks and benefits of the experimental treatment are reasonable in light of what is known about the condition and risks and benefits of other therapies.

Before the IRB may approve a protocol that has requested a waiver of consent for emergency research, the regulations require documentation of five additional protections:

- consultations with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
- public disclosure to the communities prior to initiation of the research...;
- public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study and its results;
- establishment of an independent data monitoring committee to exercise oversight of the research; and
- commitment by the investigator to attempting to contact within the therapeutic window a member of the subject's family, if feasible, and asking whether he or she objects to the subject's participation in the research.

**TAKE HOME POINT:**

Provisions exist for granting a waiver of informed consent in emergency research only when subjects in life-threatening circumstances and who cannot give informed consent are involved. Given the extensive requirements and the risk involved, a waiver of consent is rarely granted. Please contact Research and Sponsored Programs at (317) 274-8289 before submitting a study in which an emergency waiver of informed consent is being requested.

**Related Internet Links:**

[DHHS Regulations:45 CFR part 46, Section 46.10\(i\)  
\(http://infonet.welch.jhu.edu/research/joint-irb/45cfr46.htm\)](http://infonet.welch.jhu.edu/research/joint-irb/45cfr46.htm)

[FDA regulations 21 CFR Part 50 Section 50.23  
\(http://infonet.welch.jhu.edu/research/joint-irb/fda5023.htm#5023\)](http://infonet.welch.jhu.edu/research/joint-irb/fda5023.htm#5023)

## 5. RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR

The Principal Investigator (PI) is the primary individual in charge of a research study involving human subjects. As such, the PI has many responsibilities which include but are not limited to:

- management and completion of the scientific and programmatic aspects of the project;
- hiring or assigning employees and approving the selection or appointment of individuals to the project;
- ensuring the integrity and safeguarding of notebooks and scientific data;
- ensuring the consent process informs subjects of all risks and benefits so that an informed choice can be made
- adherence to research protocols and policies, and notifying the appropriate offices if changes are made to the protocol and/or informed consent statement;
- meeting continuing review requirements as established by the IRB;
- adherence to the policies, procedures and regulations for using investigational new drugs and devices for clinical research;
- reporting all serious and unexpected adverse events as they occur
- assuring compliance with all IRB policies.

### TAKE HOME POINT:

The principal investigator is ultimately responsible for the conduct of the research, including ensuring that an investigation is conducted according to the approved protocol and the applicable regulations. The PI is also responsible for protecting the rights, safety, and welfare of the subjects under the investigator's care.

### Related Internet Link:

[FDA Regulations - 21 CFR 312.60 - Responsibilities of Investigators](http://www.fda.gov/cfr/cfr.cgi?TITLE=21&PART=312&SECTION=60&YEAR=2000&YEAR=2000&TYPE=TEXT)  
(<http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=21&PART=312&SECTION=60&YEAR=2000&YEAR=2000&TYPE=TEXT>)  
<http://www.iupui.edu/%7Eeresgrad/spon/assurance.htm>

## 5.1 OTHER NECESSARY APPROVALS

In addition to IRB approval, in some instances other approvals may be necessary before research may begin. The following discusses a few of those instances. The investigator is responsible for knowing when other approvals may be necessary.

Patient research that uses facilities at the **VA or Wishard Hospitals outpatient medicine or subspecialty clinics** or recruits patients from their clinical venues requires prior review by the VA Research and Development Committee or the Wishard Research Committee. The PI should apply to these committees **after** the protocol has received IRB approval. These committees review applications monthly. The VA Research and Development Committee may be reached at 554-0000, extension 2525. The Wishard Research Committee may be reached at 278-2868.

If the research involves the use of **radiation and/or radioactivity** in addition to what is already used for standard clinical treatment or the subject would receive radiation exposure only due to participation in the research, approval must also be obtained from the appropriate radiation committee. Further information and sample risk statements for radiation exposure may be obtained from the Radiation Safety Office, Clinical Building, Room 159, 274-4797.

If the facilities of the **General Clinical Research Center (GCRC)**, University Hospital, Room 5595, will be used further research information is required for IRB submissions. Please contact GCRC at 274-0949 to obtain additional requirements **prior** to completing IRB submission. The Center must be provided with all documentation required by the IRB, i.e., protocols, amendments, ongoing reviews, etc.

Any studies at IUPUI involving **cancer patients** must be submitted to the Scientific Review Committee at the Cancer Center. Please contact the Committee at 274-0935 for applications and more information.

### TAKE HOME POINT:

The investigator is responsible for knowing if other approvals may be necessary – and securing them – before research begins.

### Related Internet Link:

<http://www.indyrad.iupui.edu/research/rrd9.htm>  
<http://www.medicine.iupui.edu/ctp>  
<http://www.gcrc.iupui.edu/>

## **6. SPECIAL PROTECTIONS FOR VULNERABLE POPULATIONS**

### **What are “vulnerable populations?”**

Vulnerable populations include individuals who may be vulnerable to coercion or undue influence to participate in research projects. They may also include research populations, or be associated with populations, that are simply unable or have limited capacity to provide “consent.” Thus, federal regulations require additional protections for special subject populations:

- Prisoners
- Children
- Pregnant Women
- Fetuses
- Cognitively Impaired

In addition, it is important to note that, in some cases, state and local laws will also be relevant in these considerations. The next several pages will explore IRB requirements associated with each type of subject population.

### **TAKE HOME POINT:**

- Some populations of research participants may be especially vulnerable to coercion or undue influence or may not be able to provide “consent.” Federal regulations require that special considerations be employed in research with these populations.

### **Related Internet Link:**

[http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter3.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter3.htm)

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm#>

## 6.1 FETUSES

### **Definition:**

A fetus is defined as *the product of conception from the time of implantation until delivery*. Once the fetus is delivered or expelled and is viable (likely to survive to the point of sustaining life independently, given the benefit of available medical therapy), it is designated as an infant and is thus subject to federal regulations governing research with children (see discussion below). The fetus should be treated respectfully and with dignity and its genetic heritage and vulnerability should be recognized, regardless of its life prospects. Because the fetus shares a unique relationship with its mother and cannot consent to be a research subject, special federal regulations are in place to guide fetal research.

In research, risks to the fetus may not be more than *minimal* (e.g., risks from ultrasound or changes in maternal diet) and if the risk to the fetus is deemed more than minimal, it must be justified by the anticipated benefit for the health of the mother or the particular fetus. It can be problematic, however, to determine what exactly is *minimal risk* for a fetus as compared to a child or adult; and IRBs and investigators should work closely to make this determination. However, if risk to the fetus is more than minimal and without anticipated medical benefit to the mother or fetus, special provisions apply, and the IRB must determine that data gained from such a study is not obtainable in any other research design or format.

Basic types of research involving fetuses include:

- **Research directed toward the fetus in utero.** An IRB can approve this kind of research if the purpose of the research is to meet the health needs of the fetus and will be conducted in such a way to minimize risk *or* if the research presents no more than minimal risk to the fetus and the purpose of this activity is the development of new knowledge that is unobtainable by any other way. As always, risks should be justified by a consideration of potential benefits.
- **Research involving the fetus ex utero.** If the fetus is judged viable outside of the uterus, then it is considered an infant and is thus governed by research regulations involving children. If a fetus is judged nonviable (unable to survive to the point of sustaining life independently), then research is forbidden.
- **Research with dead fetuses, fetal material, and placenta.** Research with dead fetuses, fetal material, or cells, tissues, or organs removed from a dead fetus are governed by state laws and regulations. Ethical considerations commonly held about respect for the dead should be observed if proposing such research.

**Fetal tissue transplantation research** is considered a special category of fetal research and will be addressed in an advanced module.

Finally, in fetal research, the consent of the mother on behalf of the fetus is required. Generally, the consent of the father is also required unless the father's identity cannot reasonably be ascertained, the father is not reasonably available, or the pregnancy resulted from rape. If a father is determined to be unavailable, investigators should document their reasons for this determination.

**TAKE HOME POINT:**

- A fetus is defined as *the product of conception from the time of implantation until delivery*. In research, risks to the fetus may not be more than *minimal*, unless such greater risk can be justified by the anticipated benefit for the health of the mother or the particular fetus. The mother provides consent for the fetus and, if available, the father should consent, too.

**Related Internet Links:**

[http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter6.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter6.htm)

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm#subpartb>

## 6.2 PREGNANT WOMEN

Research involving women who are or may become pregnant receives special attention from IRBs because of women's additional health concerns during pregnancy and because of the need to avoid unnecessary risk to the fetus. Pregnancy is defined as *the period from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (i.e., has been delivered)*.

In studies involving pregnant women, IRBs must also determine when the informed consent of the father is necessary. Additionally, because of the involvement of the fetus (who cannot give consent), the IRB must consider the need to prevent harm or injury to future members of society.

At the same time, IRBs must also recognize that the inclusion of women in research study populations is important so that research findings can be generalizable and of benefit to all persons at risk of a disease, disorder, or condition under study. The inclusion of women is also a NIH requirement. Therefore, pregnant women may be involved in several kinds of research which present differing IRB duties for each kind of research.

The three basic types of research are:

- **Studies in which pregnancy is coincidental to subject selection.** Any study where women of childbearing potential are possible subjects could inadvertently include pregnant women. These subjects should be notified that a particular treatment or procedure “may involve risks to the subject (or to the embryo or fetus if the subject is or becomes pregnant) that are currently unforeseeable.” Non-pregnant subjects may need to be advised to avoid pregnancy or nursing while involved or following the research.
- **Studies directed primarily toward the mother's health.** As women's health can be positively or negatively affected by pregnancy, some research may be undertaken to explore these issues. As such, a woman's needs generally take precedence over those of the fetus. IRBs should, however, attempt to ensure that the risks to the fetus are minimized.
- **Studies directed toward pregnancy.** Many studies are directed to examine the normal and abnormal processes of pregnancy, labor, and delivery. In these cases, the IRB must determine that the risk to the fetus is “minimal.” “Minimal” is defined as where the risk to the fetus is no more than that from established procedures routinely used in a uncomplicated pregnancy or in a pregnancy with complications comparable to those being studied. If the IRB cannot conclude that the risk is minimal, it can consult with the Secretary of DHHS. Basically, it must then be determined that the risks are far outweighed by the benefits to the subject and the importance of the knowledge to be gained.

In terms of consent, federal regulations require that both the woman's and the father's consent for research be obtained in these categories unless the purpose is to meet the health needs of the mother, the father's identity or whereabouts cannot be reasonably ascertained, he is not reasonably available, or the pregnancy resulted from rape.

**TAKE HOME POINT:**

- Inclusion of pregnant women in research study populations is important so that research findings can be generalizable and of benefit to all persons at risk of the disease, disorder, or condition under study. Generally, pregnant women can be involved in research, but the risk to the fetus should be considered "minimal."

**Related Internet Links:**

[http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter6.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter6.htm)

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm> - subpartb

## 6.3 CHILDREN

### **Definitions:**

Children are defined as *persons who have not yet attained the legal age for consent to treatment or procedures involved in research as determined by local law*. Generally, the law considers *any person under 18 years old* to be a child. An assent is defined as a *child's affirmative agreement to participate in research*. (Failure to object should not be construed as assent.)

Children are considered a vulnerable population because their physical and intellectual capacities are limited and as such, special considerations are necessary. IRBs reviewing research involving children as subjects must consider the benefits, risks, and discomforts inherent in the proposed research and assess their justification in light of the expected benefits to the child-subject or to society as a whole. Thus, when IRBs review research involving children, they are required to classify such research as involving children in one of four categories. The four categories are:

1. Research not involving greater than minimal risk.
2. Research involving greater than minimal risk, but presenting the prospect of direct benefit to the subject.
3. Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
4. Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (With this category, the IRB must consult the Secretary of DHHS and a panel of experts for concurrence.)

The principal investigator should initially determine into which category the research falls and provide a rationale for this choice upon submission of the research study to the IRB. The final determination will be made by the IRB.

### **Consent procedures:**

In research with children, written parental permission is required. If the IRB determines that the research involves greater than minimal risk, signatures from both parents are necessary. However, in some cases, the IRB may determine that it is acceptable for *only one parent* to provide permission when one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. In other cases, such as child abuse or treatment of venereal disease, parental permission may not be appropriate and here, the IRB can grant a "waiver of parental consent" if it is determined that the research will provide great benefit to the population being studied and that obtaining parental consent may put the subject at considerable risk. Permission from parents is usually indicated in a form similar to a subject consent form, constructed to request "your child" to participate.

Once parental permission has been obtained, the agreement of the child can be required by the IRB and this can be documented in an assent. An assent of the child requires that the child be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity, and condition. This explanation should also include a discussion of any discomforts and inconveniences the child may experience if he or she agrees to participate. Parental permission overrules a child's decision not to participate in therapeutic settings.

**TAKE HOME POINT:**

- Research involving children requires that the IRB make a determination about the particular category of research in which it belongs. In addition, dependent upon age, maturity, experience, and condition, children should be given the opportunity to assent their participation. Finally, one or both parents must provide permission for a child's involvement in research unless the IRB determines that parental permission may not be appropriate.

**Related Internet Links:**

[http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter6.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter6.htm)

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm#subpartd>

## 6.4 PRISONERS

According to 45 CFR 46.303(c), a **prisoner** is defined as any individual involuntarily confined or detained in a penal institution. This term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. *It is important to note that this category of special protections also includes situations where a research subject may become a prisoner after the research has commenced.*

Only certain types of research may be conducted utilizing prisoners as subjects:

- study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
- study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
- research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) the study may proceed only after OHRP has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register
- research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after OHRP has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register

Coercion is a the IRB's main focus when reviewing studies involving this population. Many factors will be taken into account regarding this issue before a study may be approved. When prisoner research is reviewed by the IRB, IRB membership in attendance at that meeting will include a prisoner representative with appropriate background and experience to serve in that capacity.

**TAKE HOME POINT:**

When an IRB reviews research involving prisoners as subjects, additional issues must be addressed by the investigator prior to the study's approval. In some cases, the study may not be approved until the research is approved by OHRP.

**Related Internet Links:**

[http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter6.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter6.htm)

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm> -  
subpartc

<http://www.iupui.edu/%7Eeresgrad/spon/prisoners.htm>

## 6.5 COGNITIVELY IMPAIRED PERSONS

### **Definition:**

A cognitively impaired person is defined as having either a *psychiatric disorder* (e.g., psychosis, neurosis, personality or behavior disorders), an *organic impairment* (e.g., dementia), or a *developmental disorder* (e.g., mental retardation) that *affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished*. In addition, persons under the influence of or dependent on drugs or alcohol, suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

Thus, the major ethical concern in research involving individuals with psychiatric, cognitive, or developmental disorders, or who are substance abusers is that their disorders may affect their capacity to understand the information presented and their ability to make a reasoned decision about participation. Also, many individuals with such disabilities may be residents of institutions responsible for their total care and treatment and this factor may have an impact on or further compromise these individuals' ability to exercise free choice (voluntariness) in participating in research. (For example, these individuals may agree too readily to requests for their "cooperation" or may be vulnerable to perceived or actual pressures for fear of being denied services.) It is for these reasons that special protections must be considered by the IRB when reviewing research involving cognitively impaired persons.

When reviewing research involving cognitively impaired persons, the IRB must consider several issues:

- Do such individuals comprise the only appropriate subject population? In other words, do the research questions focus on issues unrelated to their disorders or institutionalization?
- Are there sufficient protections for privacy and confidentiality of information gathered?
- How are issues of consent and competence addressed? As a general rule, there should be specific evidence of individuals' incapacity to understand and to make a choice before they are deemed unable to consent. When individuals are deemed unable to consent, investigators and IRBs must seek legal advice to consider state and local laws governing the selection of an appropriate representative to consent on behalf of these individuals. IRBs should also consider the possibility of obtaining "assent" (see the discussion on involving children in research) from potential research participants.

**TAKE HOME POINT:**

- Cognitively impaired persons are defined as having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders), an organic impairment (e.g., dementia), or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. When reviewing research with these populations, IRBs have a variety of issues to consider to ensure that such potential research participants are protected.

**Related Internet Links:**

[http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter6.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter6.htm)

## 7. IRB REVIEW OF MODIFICATIONS TO PREVIOUSLY APPROVED RESEARCH STUDIES: AMENDMENTS

Amendments are defined as *any changes to a research protocol initiated by the PI or the sponsor* and investigators are required to report any proposed changes whatsoever to their research. Thus, it is the responsibility of the PI to notify the IRB via an amendment form when any changes occurring after final approval are proposed. Proposed changes in research studies may not be initiated until the investigator receives notification of IRB approval of the amendment.

At IUPUI, amendments can be classified in one of two ways:

- **Minor:** A minor amendment is one of minimal risk to the subject. Examples of minor amendments include title or PI changes, the addition of co-investigators, additions of or changes to advertisements, dose reductions, a decrease in the amount of blood drawn, extending the period for recruiting subjects or adding the audiotaping of subjects. Minor amendments do not have to be reviewed in a convened IRB meeting, but can be reviewed by IRB reviewers on a weekly basis and are thus referred to as being **“expedited.”**
- **Major:** A major amendment is considered substantive in nature. Examples of major amendments include any change presenting increased risk to the subject, an increase in the amount of blood drawn, safety issues, multiple changes in study design, increased dosages, adding additional subjects, extending the duration of a study, additional radiation exposure, or the videotaping of subjects. Major amendments are reviewed in convened IRB meetings and are thus referred to as being subject to **“full review.”**

At IUB, amendments to studies which initially were approved by the full IRB are also reviewed by the full IRB. Amendments to studies which were reviewed on an expedited basis and which involve no more than minimal risk are also handled on an expedited basis.

It is important to note that the above-mentioned examples are presented as general guidelines only. Specific amendment classifications are made on a case-by-case basis. The practical result to investigators is that amendments subject to expedited review can typically be handled in one week, while amendments subject to full review will be considered at the regularly-scheduled meeting of the full IRB (once a month).

### TAKE HOME POINT:

- It is the responsibility of the PI to notify the IRB of any proposed changes to a research project via an amendment. Amendments can be classified by the IRB as either major or minor and any proposed changes may not be implemented until IRB approval has been granted.

**Related Internet Links:** <http://www.iupui.edu/~resgrad/spon/amendfor.rtf>

## 8. CONTINUING REVIEWS

IRB approval is a continuing process. Only after research has begun can the real risks be evaluated and the risk/benefit ratio assessed. For these reasons, upon the time of final approval of a research project, the IRB makes a determination about how often to reevaluate a research project and sets a date for its next review. According to federal regulations, all research must be reviewed at least annually and each of these subsequent reviews is referred to as a “continuing review.”

Continuing review forms are generated for PIs by the R&SP and HSC offices. This status report must be completed even if the study was never initiated or was terminated for any reason. If a PI leaves the Institution, the IRB must be notified as to the disposition of each study. Once the appropriate forms are received and processed, the IRB reviews the status of the research project and reassesses any new findings, new knowledge, or adverse events that may affect the risk/benefit ratio. If necessary, the IRB can require that new information be communicated to research participants (via the informed consent document), that the study be modified in some way, or that the research be stopped entirely.

Continuing Reviews are classified by the IRB in two ways:

- Certain types of research are subject to **expedited review**. Examples of expedited continuing reviews include minimal risk studies or research which is permanently closed to subject enrollment. Expedited reviews do not have to be conducted during a convened IRB meeting, but can be examined on a weekly basis by IRB reviewers.
- All other types of research require **full review** by the IRB as long as investigators are either interacting or intervening with subjects for research purposes, or are accessing *identifiable private information* for research purposes. **Private information** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place. Information is **identifiable** when the identity of the subject is or may readily be determined by the investigator or can be associated with the information.

PIs also use continuing review to notify the IRB that a study is being terminated. When a study is being terminated at any time other than at its continuing review, PIs should call the R&SP or HSC office to request this form and it will be generated for the PIs completion.

### TAKE HOME POINT:

- IRB approval is an ongoing process and IRBs must review research at least on an annual basis. The status of a research project is communicated to the IRB via a continuing review form. If necessary, after review, the IRB can require that new information be communicated to research participants (via the informed consent document), that the study be modified in some way, or that the research be stopped entirely.

**Related Internet Links:** <http://www.iupui.edu/~resgrad/spon/download.htm>

## 9. ADVERSE EVENT REPORTING

An adverse event is an unanticipated negative effect. Investigators must report any adverse event associated with the use of experimental drugs, devices, or procedures that is

- serious **OR** unexpected
- AND**
- possibly related to the intervention.

These events must be reported to the IRB within **three (3) working days** after the incident if the incident happened on-site. If the incident occurred at another site involved in a multi-center study, the incident only needs to be reported to the IRB if it is

- serious
- AND**
- unexpected
- AND**
- possibly related to the intervention.

These events must be reported to the IRB within **five (5) working days** of receipt from the sponsor. A form must be filled out for each event. All other reports not falling into these categories may be reported at the time of continuing review.

For definitional purposes, any event that

- is fatal
- is life-threatening
- is permanently/significantly disabling
- requires or prolongs hospitalization
- causes a congenital anomaly
- requires intervention to prevent *permanent* impairment or damage

is considered a serious adverse event.

An adverse event is **unexpected** if it is not identified by nature, severity or frequency in the current lay summary of the protocol and the informed consent document.

When these adverse events are reported, at the discretion of the IRB, the informed consent may be required to include updated risk information and/or the study may be suspended until it is assured that continuing the research will not jeopardize future subjects.

In addition, studies involving human gene transfer research have more stringent reporting requirements. All serious events must be reported immediately regardless of whether they are related to the intervention or expected.

**TAKE HOME POINT:**

There are specific reporting requirements for adverse events depending upon the location of the event, the type of event, the relationship to the study intervention, and the type of study. The IRB may require the consent form to be updated and may even suspend the study if it is felt that the risks are too great.

**Related Internet Link:**

<http://www.iupui.edu/%7Eeresgrad/spon/adverserequire.htm>

## 10. PROTOCOL DEVIATIONS

PIs are responsible for conducting human subjects research in compliance with federal laws and regulations, the institution's commitments and policies, and standards of professional conduct and practice. Failure to comply with regulations can result in loss of funding to do human subjects research or the annulment of the investigator's privilege to do the research even if funded. Non-compliance by one investigator can affect the ability of all others at the institution to do human subjects research.

Examples of noncompliance include:

- failure to obtain/maintain approval for research,
- failure to obtain informed consent when required,
- failure to file adverse event reports,
- performance of an unapproved study procedure,
- performance of research at an unapproved site,
- failure to file protocol modifications, and failure to adhere to an approved protocol.

These examples of non-compliance are often referred to as protocol deviations.

Investigators can almost always avoid protocol deviations by being aware of the IRB requirements and following the approved protocol. Once a study is approved, an amendment form must be completed before any change is implemented in the protocol. If a protocol deviation does occur, the PI must report it to the IRB immediately upon discovery.

### **TAKE HOME POINT:**

Protocol deviations not only jeopardize an investigator's research program, but can jeopardize the research conducted throughout the institution. No change from an approved protocol should be implemented before final written approval is received from the IRB.

### **Related Internet Link:**

<http://www.iupui.edu/~resgrad/spon/amendfor.rtf>

## 11. CONTACT INFORMATION

For any questions regarding this course or for any other information, please contact the Institutional Review Board Offices at your campus listed below:

### **At IUPUI:**

Research and Sponsored Programs  
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### **At IUB:**

Human Subjects Committee  
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<http://www.indiana.edu/~resrisk/operate.html>

### **At Methodist Hospital:**

Methodist IRB Office  
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### **AT IUK:**

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