Protection of Human Subjects in Non-Biomedical Research: A Tutorial

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Contents

This tutorial is adapted from “Protection of Human Subjects in Research” by Shelley Bizila, Director of Research Compliance, Research and Sponsored Programs, Indiana University/Purdue University-Indianapolis (2000). This version was prepared by Kenneth D. Pimple, Ph.D., in consultation with the Human Subjects Protection Education Committee of Indiana University. Care has been taken to ensure the accuracy of the information herein, but it should be noted that this tutorial is not a policy statement.

1 Who should take this tutorial?

Indiana University offers two tutorials for the protection of human subjects in research. This tutorial focuses on non-biomedical research with human subjects – generally speaking, research in the social and behavioral sciences, education, and the humanities.

Virtually all of the issues covered in this tutorial also apply to biomedical research with human subjects. An earlier tutorial, "Protection of Human Subjects in Research," also covers issues related to physical interventions.

Unfortunately the ethical concerns associated with human subjects research do not map neatly onto discipline. For the purposes of these tutorials, the dividing line between "biomedical" and "non-biomedical" research is drawn just beyond the subject's body. Research that requires the touching or invasion of the subject's body, including the use of electrocardiograms, blood draws, the ingestion of drugs, and the like, or in which the risk of harm to the research subject includes physical harm, is here considered biomedical research.

This tutorial is thus directed toward research that does not require contact with or invasion of the subject's body and in which the risk of harm to the research subjects is social or psychological in nature, including embarrassment, stigmatization, legal liability, and damage to reputation.

2 Objectives

The core objective of this tutorial is to ensure that human subjects of non-biomedical research undertaken at Indiana University are treated with respect and protected from harm. To this end the tutorial describes the ethical principles guiding human subjects research in the United States and the regulatory framework built upon the foundation of those principles.

In particular, upon successful completion of this tutorial, you should be able to:

1. Describe the historical events that led to the current regulatory environment for the protection of human subjects in research, including the importance of the Belmont Report and the three ethical principles it delineates (respect for persons, beneficence, and justice).

2. Explain the definitions of "human subject" and "research" according to the Department of Health and Human Services (HHS).

3. Describe the role of the Institutional Review Board (IRB) in research oversight.

4. Describe the process of IRB review, including the responsibilities of the researcher to submit research protocols and the actions that an IRB can take to enforce regulations.
5. Describe the basic differences between “exempt,” “expedited,” and “full” IRB review.
6. Describe the informed consent process in research with human subjects, including the circumstances in which the requirement for securing informed consent or for documenting informed consent can be waived.
7. Describe the responsibilities of the Principal Investigator (PI) in protecting human subjects.
8. Describe the special populations that require additional protections in research and the nature of those protections.
9. Describe the processes for amending previously approved research protocols, for continuing review of research, and for reporting unanticipated problems.

3 A 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, the Food and Drug Administration (FDA) did not yet exist, the Common Rule had not been written, and the Institutional Review Board (IRB) system had not been established to oversee research. What follows is a brief discussion of why Federal rules and regulations were established and why the IRB system became a necessity.

3.1 Abuses in Biomedical Research

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.

In 1972, nearly a quarter of a century after the Nuremberg Code was adopted, the U.S. Public Health Service (PHS) Syphilis Study at Tuskegee (commonly referred to as the Tuskegee Study) became widely known. Beginning in 1932, 600 low-income African-American males, 399 of whom were infected with syphilis, were monitored for 40 years in an effort to understand the

progression of untreated syphilis in "the Negro." Although the subjects had more freedom than the victims of the Nazi experiments, their consent to take part in the study was not informed and can scarcely be considered free or voluntary in any meaningful sense. They were routinely deceived about the study and told they were being treated when, in fact, they were not.

Study subjects received free medical examinations, but 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 on May 16, 1997.

- ***Take Home Point***
  The Nazi experiments and the PHS Study of Syphilis at Tuskegee are only two examples of abusive biomedical research projects involving human subjects. Many others could be cited. These terrible events made it clear that biomedical science was not adequately monitoring research and that outside oversight was necessary.

- ***Related Internet Links***
  The IRB Guidebook, Appendix 6, The Nuremberg Code – http://www.hhs.gov/ohrp/irb/irb_appendices.htm#j5

  "The Troubling Legacy of the Tuskegee Syphilis Study" describes a symposium held in 1994 entitled "Doing Bad in the Name of Good? The Tuskegee Syphilis Study and its Legacy." See http://www.med.virginia.edu/hs-library/historical/apology/index.html.

  President Clinton's apology can be found at http://clinton4.nara.gov/textonly/New/Remarks/Fri/19970516-898.html.

3.2 Abuses in Non-Biomedical Research

Some of the most controversial studies in non-biomedical research were designed or inspired by social psychologist Stanley Milgram. In the early 1960s, Milgram, performed a series of experiments while he was at Yale and Harvard intended to elucidate how millions of ordinary Germans could have actively and passively participated in the Holocaust. His "obedience to authority" studies showed that ordinary Americans would follow orders to harm or kill a stranger. The subjects were made to think that they were inflicting harm when in fact they were not, and experienced tremendous stress during and after the experiment. The abstract of one of Milgram's first publications on the study[1] describes the experiment this way:

[1] Milgram, Stanley. 1963. "Behavioral study of obedience." Journal of Abnormal and Social Psychology 67(4):371-378.

> It consists of ordering a naïve S [subject] to administer increasingly more severe punishment to a victim in the context of a learning experiment. Punishment is administered by means of a shock generator with 30 graded switches ranging from Slight Shock to Danger: Severe Shock. The victim is a confederate of the E [experimenter]. The primary dependent variable is the maximum shock the S is willing to administer before he refuses to continue further. 26 Ss obeyed the experimental commands fully, and administered the highest shock on the generator. 14 Ss broke off the experiment at some point after the victim protested and refused to provide further answers. The procedure created extreme levels of nervous tension in some Ss. Profuse sweating, trembling, and stuttering were typical expressions of this emotional disturbance.

In 1972, the Stanford Prison Experiment put subjects under similar kinds of stress when Philip G. Zimbardo and colleagues at Stanford University randomly assigned twenty-four young men to play the role of prisoner or prison guard in what was to be a two-week simulation of prison life. The researchers suspended the study after 6 days "because of what the situation was doing to the college students who participated. In only a few days, our guards became sadistic and our prisoners became depressed and showed signs of extreme stress."

- ***Take Home Point***
  Milgram's obedience to authority studies and Zimbardo's prison experiment are dramatic examples of the harms that can be inflicted upon human subjects in non-biomedical research. Many less extreme cases have been documented.

- ***Related Internet Link***
  A chilling slide show of the Stanford Prison Experiment can be found at http://www.prisonexp.org/.

3.3 The National Research Act and the Belmont Report

Largely due to the publicity from the Tuskegee Syphilis Study, the United States Congress passed the National Research Act of 1974. The 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.

In 1979, the National Commission published the Belmont Report, which elucidates three fundamental ethical principles that should guide research with human subjects. Each principle is supplemented by a characteristic practical application. The Belmont Report became a foundational document for the ethics of human subjects research in the United States.

The first principle described in the Belmont Report is respect for persons. This principle demands respect for the autonomy of human subjects as self-determining agents. Their rights, including the right to privacy and to self-determination, should be upheld. It also specifies that persons with diminished autonomy (such as children and prisoners) must be afforded additional protections. The primary application of the principle of respect for persons is informed consent, a

process by which potential human subjects of research are provided adequate information about the research to enable them to comprehend the implications of participating in the research. Participation as a research subject must also be completely voluntary.

The second principle is beneficence. Researchers should not harm human subjects, and studies should maximize possible benefits and minimize possible harms. In order to honor this principle, researchers must carry out a risk-benefit analysis, systematically assessing the nature and scope of risks and benefits associated with the research. This assessment must be shared with potential subjects.

The third principle is justice, which specifies that the risks and benefits of research should be distributed fairly. It is unfair, for example, if the burden of research is carried by poor people when everyone, rich and poor, can benefit from the results. Clearly, justice is ensured through an equitable method of selection of subjects. Individual subjects or social groups should not be selected for beneficial research because of their perceived social "desirability," nor should they be selected for risky research because of their perceived "undesirability."

- ***Take Home Points***
  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.

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

- ***Related Internet Link***
  The Belmont Report – http://www.hhs.gov/ohrp//humansubjects/guidance/belmont.htm.

4 Current Regulations

In 1981, the Department of Health and Human Services (HHS) Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of human subjects), which was based on the Belmont Report, became law.

In 1991, the core HHS regulations (45 CFR 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; and

- additional protections for certain vulnerable research subjects – pregnant women, prisoners, and children

➢ ***Take Home Point***
The Common Rule (45 CFR 46) provides protections for human subjects in research and mandates IRB oversight of such research.

➢ ***Related Internet Link***
The Common Rule (45 CFR 46) –
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

4.1 Federalwide Assurance

Within HHS, the Office for Human Research Protections (OHRP) provides leadership on human research subject protections and implements a program of compliance oversight for the Common Rule. In keeping with the provisions of the Common Rule, each institution funded by any HHS agency must have an OHRP-approved assurance of compliance with HHS regulations. These assurances are known as Federalwide Assurances (FWA).

A Federalwide Assurance is an institution's pledge of full human subject protections for multiple projects at the institution. Indiana University holds such an Assurance. This assurance identifies the institution's responsibilities and explains the steps that it will take to meet the Federal regulations for research on human subjects. Indiana University's Federalwide Assurance requires that all research projects involving human subjects, regardless of funding source, conducted by an employee of the institution, in this case, Indiana University or Clarian Health Partners, must 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 OHRP to suspend or revoke the Assurance for the entire institution. Therefore, it is important that all investigators be knowledgeable about the contents of the FWA.

➢ ***Take Home Point***
Indiana University and Clarian Health Partners, through their FWAs, have pledged to protect human subjects and comply with all relevant Federal regulations with respect to all human subjects research, whether funded or unfunded, and regardless of the source of funding.

➢ ***Related Internet Links***
Information about Federalwide assurances held by Indiana University, Clarian Health Partners, and institutions listing an IU or Clarian IRB on their assurance can be found at
http://www.iupui.edu/%7Eresgrad/spon/fwa.htm

General information on Federalwide and other assurances can be found at
http://www.hhs.gov/ohrp/assurances/assurances_index.html

4.2 Enforcement of the Regulations in Non-Biomedical Research

If there was ever any doubt that the Federal government was serious about enforcing the regulations concerning human subjects protection in non-biomedical research, that doubt vanished in January 2000 when the Office for Protection from Research Risks (which was later renamed the Office of Human Research Protections, or OHRP) suspended all human subjects research at Virginia Commonwealth University.

The suspension resulted from a complaint about a survey. The case "involved the father of a research participant who complained to federal officials that a VCU genetics study asking his daughter questions about her family history was an invasion of his family's privacy" (The Scientist 14(9):1, May. 1, 2000).

The suspension only lasted a month, but it was highly disruptive to researchers and research projects across VCU.

- ***Take Home Point***
  Violations of the regulations concerning human subject protection can have serious consequences to the researcher and the researcher's institution.

- ***Related Internet Link***
  "Case at VCU Brings Ethics To Forefront," The Scientist 14(9):1, 1 May 2000 – http://www.the-scientist.com/yr2000/may/amber_p1_000501.html

  "U.S. Suspends Human-Subject Research at Virginia Commonwealth U," The Chronicle of Higher Education 28 January 2000 p. A33 – http://chronicle.com/prm/weekly/v46/i21/21a03302.htm

4.3 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 "systematic investigations" may involve various invasive or non-invasive procedures including 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 investigation is undertaken with the intention of publishing or presenting the findings in some form or forum outside of the institution. For example, if the project is undertaken with the expectation that it will be published in a journal or presented orally or as a poster at an academic conference or community gathering, that 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 undertake a project with the intention of publishing the results, 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***
  The Common Rule's section on definitions can be found at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102

  HHS has provided extensive guidance on 45 CFR 46 in the form of Protecting Human Research Subjects: Institutional Review Board Guidebook, commonly referred to simply as the IRB Guidebook. The Guidebook can be ordered at http://www.hhs.gov/ohrp/references/irb_orderform.htm or read at http://www.hhs.gov/ohrp/irb/irb_guidebook.htm

4.4 What is a Human Subject?

- ***Definitions***
  "Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information."

  "Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes."

  "Interaction includes communication or interpersonal contact between investigator and subject."

  "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, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects."

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 asked to fill out a survey or questionnaire

- ***Take Home Point***
  A human subject is any individual about whom an investigator obtains data through intervention or interaction or obtains 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 link***
  45 CFR 46, "Definitions – Human Subject" –
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102

4.5 Some Equivocal Cases

The Federal definition of "research" is narrower than our everyday use of the term. In some cases it can be difficult to make the determination that an undeniable research project (in the broad sense) also counts as research in this narrow sense and is, therefore, subject to Federal regulations and IRB oversight. Several such apparently equivocal cases are common in university settings.

4.5.1 Oral History

There has been some controversy over whether oral history research is intended to "develop or contribute to generalizable knowledge," a point upon which there does not seem to be a consensus even among oral historians. It is clear, however, that as a point of simple courtesy and research ethics, oral historians should always follow many of the guidelines laid down by the Federal government. At the least, oral historians should actively respect the people they work with by taking care not to put them at risk of harm and by securing their informed consent before data collection begins.

Oral historians and members of the IU community who do similar work should not take it upon themselves to decide whether their work is covered by the Federal regulations guiding research with human subjects; they should consult with the relevant IRB before data collection begins.

- ***Related Internet Links***
  "Federal Agency Says Oral-History Research Is Not Covered by Human-Subject Rules," The Chronicle of Higher Education 31 October 2003 p. A25 –
  http://chronicle.com/prm/weekly/v50/i10/10a02501.htm

  Oral History Association, "Oral History Excluded from IRB Review" –
  http://www.dickinson.edu/oha/org_irb.html

4.5.2 Quality Improvement, Quality Assurance

At times, members of the IU community are asked to assist in quality improvement or quality assurance work (though it is not always identified under these terms). For example, if a local school system wants to improve its nutrition, it might contract with one or more IU researchers to find out what students currently eat. If the results of the study are made available only to the school system, such a study cannot be construed as "developing or contributing to generalizable

knowledge" and does not require IRB approval. Of course, this does not excuse researchers from showing adequate respect for the people they study and executing their work with high ethical standards.

However, if the IU researchers wish to analyze the data and publish it as research, they must seek IRB approval before data collection begins.

- ***Related Internet Link***
  Institute of Medicine. 2000. Protecting data privacy in health services research. Washington, DC: National Academy Press. Available online at http://books.nap.edu/html/data_privacy/

4.5.3 IU Classroom Assignments

Since classroom assignments typically are neither intended to, nor likely to, lead to generalizable knowledge, the IRB does not normally include these projects under its operational definition of research. However, if the student and/or instructor plans to present and/or publish work involving human subjects outside of the bounds of the institution, the student work is considered research with human subjects and requires IRB oversight.

When a classroom assignment involving human subjects does not fit the definition of "research," there are still some circumstances in which such work requires IRB approval before it can be undertaken.

At IUB, IRB oversight is required for student work involving human subjects that (a) may expose subjects to greater than minimal risk or (b) involve special populations such as prisoners or minors.

At IUPUI, IRB oversight is required for student work involving human subjects that (a) may expose subjects to greater than minimal risk and (b) involve special populations such as prisoners or minors.

(See Section 7, Special Protections for Vulnerable Populations.)

- ***Definition***
  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.

Any type of student work may conceivably count as research with human subjects, including classroom or independent study projects, theses, and dissertations.

Instructors are responsible for screening individual student projects and making an initial determination as to whether the project may fall in the category of research as defined herein (see Section 4.3 What is Research?). If an instructor determines that a student project is characterized by one or more 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.

- ***Take Home Point***
  Any student research project that places subjects at risk, is undertaken to contribute to generalizable knowledge, or involves special populations must be reviewed and approved by the appropriate IRB before the research begins.

- ***Related Internet Links***
  IUPUI – SOP on Student Projects – http://www.iupui.edu/~respoly/human-sop/human-sop-index.htm

  IUB – Student Research – http://www.research.iu.edu/rschcomp/stures.html

4.5.4 Existing Data

Some research requires IRB oversight even though the researcher never observes or interacts with any human subject, such as when the research concerns existing data – such as medical records or publicly-available databases – about human beings.

If the data set includes private information that can be linked to an individual (i.e., the person is identifiable), IRB oversight is probably required.

Sometimes researchers collect data as part of a non-research activity, such as teaching or quality improvement/quality assurance work (see Section 4.5.2 Quality Improvement, Quality Assurance) without IRB approval. This is perfectly appropriate as long as the data collection cannot be construed as "research" with "human subjects" under the Federal guidelines. However, at times researchers later realize that the data could be used to "develop or contribute to generalizable knowledge" and apply to the IRB for approval to use the data in a research project.

In such cases, IRBs are likely to be resistant to classifying data as "existing" unless the data were collected under conditions as rigorous as those required for human subjects research –informed consent was obtained, the persons providing the data were told that the data would be used as part of a research project, the risks and benefits involved were explained, and so forth. To give ready approval to such projects would circumvent the regulations and fail to protect human subjects.

- ***Take home point***

Research with existing data sometimes does not fall under the purview of the IRB, but what counts as existing data has to be interpreted in the light of the IRB's mandate to protect human subjects.

- ***Related Internet links***
  The IUB definitions of "existing data" can be found at http://www.research.indiana.edu/rschcomp/defini.html

  The IRB Guidebook, Chapter 2, Section A.ii, "45 CFR 46: Most Frequently Asked Questions" – http://www.hhs.gov/ohrp/irb/irb_chapter2.htm#d3 (see question 11).

  45 CFR 46.101(b)(4), "To what does this policy apply?" – http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.101

5 An Overview of the Institutional Review Board (IRB) System

All institutions, including hospitals, universities, research centers, and the like, where Federally regulated research with human subjects takes place must have one or more Institutional Review Boards to protect the rights and welfare of human participants in research undertaken at that institution. 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, complaints made by human subjects, and possible violations of external regulations or institutional policies. IRBs also conduct continuing review of research at regular intervals (at least annually), and IRBs assess proposed changes in research activities or plans.

IRBs review research projects to provide for the protection of subjects against undue or unnecessary invasion of privacy, disregard for human dignity, and physical, psychological or social harm. In most cases, this involves approval of an informed consent document written in a language that is understandable to the research subject or representative. The informed consent document 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; and
- there is proper informed consent and documentation of informed consent.

In some instances, IRB review can also require that

- the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data;[2] and
- additional safeguards are included 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 informed consent process and the research.

[2] For example, in research involving surveys, interviews, or questionnaires, the IRB will scrutinize requests for identifiers (such as the subject's name, address, social security number, and the like) and suggest that these items should not be collected unless absolutely necessary.

- 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***
IRBs 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 Links***
Research at Indiana University – Research Compliance – Protection of Human Subjects – http://www.research.indiana.edu/rschcomp/human.html

The IRB Guidebook – http://www.hhs.gov/ohrp/irb/irb_guidebook.htm

45 CFR 46.111 (Criteria for IRB approval of research) – http://www.hhs.gov/ohrp//humansubjects/guidance/45cfr46.htm#46.111

5.1 IRB Composition

IRBs must have at least five (5) members with a variety of backgrounds and expertise needed to provide an adequate and complete review of the research under its purview.

Each IRB must be sufficiently qualified through the experience and expertise of its members adequately to consider issues associated with gender, racial and cultural heritage, and community attitudes. One or more members of an IRB must be knowledgeable about and experienced in working with vulnerable categories of subjects, including children, prisoners, pregnant women, or handicapped or mentally disabled persons if research involving these populations are to be reviewed. Finally, every IRB must 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.

Members of all IRBs in the Indiana University system are recommended for appointment by the Chancellor and appointed by the Vice President for Research.

A researcher usually applies to the IRB on her or his campus. However, if a researcher at one IU campus performs research at a different IU campus or a research team has members on more than one IU campus, the PI should refer to the "IRB Policy for Studies Conducted on Multiple Campuses" for more guidance (see link, below).

➢ ***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 Links***
Indiana University Office of the Vice President for Research – http://www.research.indiana.edu/

The IRB Guidebook, Chapter 1, "Institutional Administration" – http://www.hhs.gov/ohrp//irb/irb_chapter1.htm

Indiana University – IRB Policy for Studies Conducted on Multiple Campuses – http://www.research.indiana.edu/rschcomp/revlocation.html

5.2 IRB Actions

When a study is reviewed by an IRB, four possible actions can be taken:

1. Final approval – There are no changes needed in the study and the investigator can proceed with the research without further delay.

2. Provisional approval – There are minor revisions that need to be made, but full review of the changes is not required by the IRB. After the revisions are completed, the study can be reviewed and approved by the IRB Chair or a designee.

3. Tabled – The IRB has major concerns with the study. The investigator must address all of the reviewers' concerns and the study must be reviewed again by the full IRB.

4. Disapproved – The study may not be resubmitted unless completely revised. Specific reasons for disapproving research will be communicated to the investigator.

➢ ***Take Home Point***
Actions that the IRB will take on a study depend upon the adequacy of the protocol's protections for human subjects. Extensive changes may be necessary.

5.3 Levels of Review

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

- exempt from continuing IRB review,
- expedited IRB review, and
- full IRB review.

Note that the level of review is determined by the IRB, not the investigator.

5.3.1 Exempt Review

When 45 CFR 46 was drafted, investigators were allowed to determine whether their own research was exempt from all IRB review. Unfortunately, several problems became evident; researchers tend to underestimate the risks and overestimate the benefits of their own research, and many researchers are not adequately informed about the regulations. Therefore, according to

Federal guidance, institutions must have a clear policy on who shall determine what research is exempt.

Indiana University's policy requires researchers to file an application to the IRB requesting that a project be classified as exempt from continuing review. If the project does not qualify as exempt, it is returned to the investigator with the appropriate application forms. Types of research which may fit into exempt categories include, but are not limited to:

- Research on instructional strategies conducted in established or commonly accepted educational settings.
- Research 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 (see Section 4.5.4 Existing Data).
- Research and demonstration projects, which are conducted by or subject to the approval of department or agency heads.

Even when a research project falls under one of the above categories, the use of audio or video recording will require expedited review (see below) if the subjects can be identified from the recording and the recording places the subjects at risk of criminal or civil liability or damage to their financial standing, employability, or reputation.

➢ ***Take Home Point***
Even if an investigator believes that a project is exempt, she or he must submit an application to the IRB Office for a final determination.

➢ ***Related Internet Link***
45 CFR 46.101, "To what does this policy apply?" –
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.101

5.3.2 Expedited Review

Research activities that present no more than minimal risk to human subjects, and involve only certain specified procedures may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110.

➢ ***Definition***
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.

Procedures approved in the Federal regulations for expedited review that are likely to be undertaken by non-biomedical researchers include, but are not limited to:

- Recording of data from subjects using noninvasive procedures;
- Voice recording;
- Moderate exercise by healthy volunteers;

- Study of identifiable[3] existing data; and
- Research on an individual or group behavior that involves no manipulation of the subjects and is not stressful.

Interviews and surveys that include questions on sensitive topics, including sexual, stigmatizing, or illegal behavior, are often considered to pose more than minimal risk to the subject. In such cases, the risks include embarrassment or stress during the study and the potential for harm should confidentiality be breached.

Research protocols that fall under this category do not require review by the full IRB; instead, a sub-committee reviews the protocols.

➢ ***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.

➢ ***Related Internet Link***
OHRP guidance, "Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure" – http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm

5.3.3 Full Review

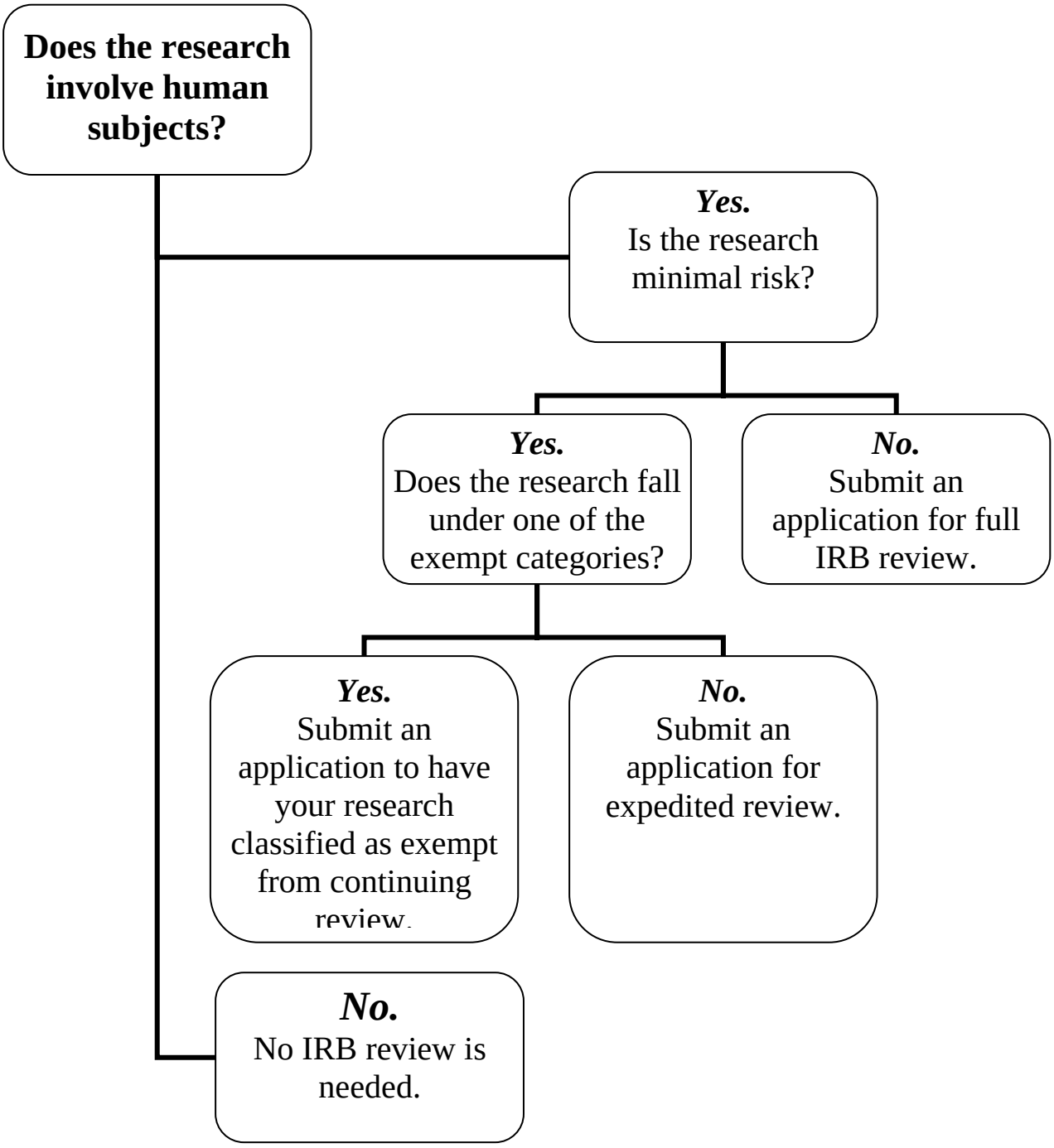
Research that involves greater than minimal risk requires review and approval by a full IRB composed of members qualified to review research in that field. Risks to research subjects posed by participation in research should be justified by the anticipated benefits to the subjects or society. Research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

- Certain types of research involving children or the cognitively impaired;
- Most research involving prisoners;
- Survey research that involves sensitive questions or is likely to be stressful for the subject; and
- Any research project that does not fit into the exempt or expedited categories.

➢ ***Take Home Point***
If any of the above-mentioned types of research is being proposed, review and approval is required by a full IRB.

[3] In this context, "identifiable" means that the existing dataset includes identifying information, such as personal names, birth dates, Social Security Numbers, etc.

5.4 Research Decision Tree



5.5 Responsibilities of All Researchers

All researchers 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 and failure to adhere to an approved protocol can result in loss of funding for human subjects research, annulment of the researcher's privilege to perform research even if funded, and a variety of other sanctions. Violations by one researcher can have serious consequences for the entire University (see Section 4.2 Enforcement of the Regulations in Non-Biomedical Research).

Examples of violations include, but are not limited to:

- failure to ensure that potential subjects are informed about all risks and benefits of participating in the research;
- performance of an unapproved study procedure;
- performance of research at an unapproved site;
- failure to maintain subject confidentiality in accordance with the protocol; and
- failure to adhere to an approved protocol and all relevant policies.

Violations such as these are referred to as noncompliance or protocol deviations.

To avoid violations such as these, researchers should be aware of the IRB requirements and follow the approved protocol. Once a study is approved, the Principal Investigator (PI) must file an amendment form before any change is implemented in the protocol (see Section 8.1 Amendments). Researchers have a responsibility to report instances of noncompliance and protocol deviations to the PI, and the PI must report them to the IRB per the appropriate campus policy. Consult the policy for your campus (see link below) for details.

- ***Take Home Point***
  Noncompliance and protocol deviations not only jeopardize an investigator's research program, but can jeopardize the research conducted throughout the institution; they must be reported to the IRB per the appropriate campus policy.

- ***Related Internet Link***
  Research at Indiana University – Research Compliance – Protection of Human Subjects – http://www.research.indiana.edu/rschcomp/human.html

5.6 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:

- managing and completing 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;
- obtaining IRB approval for research before data collection begins;
- maintaining documentation of approval for research (including all approved IRB forms and written communications with the IRB);
- meeting continuing review requirements as established by the IRB;
- reporting all unanticipated problems involving risks to subjects, protocol deviations, subject complaints, and instances of non-compliance in a timely fashion (see Section 8.3 Reporting Unanticipated Problems);
- assuring compliance with all relevant ethical standards and policies not mentioned here; and
- ensuring that all research personnel working on the project, (including the PI) fulfill their ethical and regulatory responsibilities (see Section 5.5 Responsibilities of All Researchers).

In addition to IRB approval, in some instances other approvals may be necessary before research may begin. The investigator is responsible for knowing when other approvals may be necessary. For example, patient research using the facilities at the VA Hospital, Wishard Hospital, or the General Clinical Research Center require additional approvals before research can begin.

➢ ***Take Home Point***
The principal investigator is ultimately responsible for the conduct of all members of the research team, 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 her or his research subjects.

6 Informed Choice

Informed consent is the primary application of the ethical principle of respect for persons (see Section 3.3 The National Research Act and the Belmont Report).

Informed consent is an ongoing process and assures that prospective human subjects will understand the nature of the research in which they have been asked to participate and can knowledgeably and voluntarily choose whether or not to participate. A robust informed consent process protects all parties involved – the subject, whose autonomy is respected, and the investigator, who otherwise may face legal hazards.

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. The investigator should do anything necessary 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 burden of ensuring that a prospective research subject has been adequately informed about the research and takes part freely 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 goal of the informed consent process is to ensure that potential research subjects are able to make a free and informed choice about participating in a research project. The process does not end with the signing of the consent statement.

- ***Related Internet Link***
  The IRB Guidebook, Chapter 3, Section 3, "Informed Consent" – http://www.hhs.gov/ohrp/irb/irb_chapter3.htm#e2

6.1 The Informed Consent Statement: The Essentials

The Federal regulations require that certain information must be provided to prospective research participants when applicable. The basic requirements are:

- A statement that the study involves research.
- An explanation of the purposes of the research.
- The expected duration of the subject's participation.
- A description of the procedures to be followed.
- Identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
- For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained.

- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of research-related harm to the subject.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled.

The informed consent statement must be written in a language that is understandable to the subject population. IU recommends informed consent statements be written at the 8th grade reading level.

Finally, the informed consent statement must not contain any exculpatory language. In other words, subjects must 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 essential tool for communication between an investigator and a potential research participant. Federal regulations require the inclusion of several elements and specify that the consent statement must be written in language that is understandable to the subject population, should include the facts a subject might want to know before deciding whether or not to participate in the research, and should not contain any exculpatory language.

➢ ***Related Internet Links***
OHRP's "Informed Consent Checklist" can be found at
http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm

6.2 The Informed Consent Statement: Additional Requirements

Depending upon the nature of treatments or procedures 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:

- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent (for example, if during the course of an interview the subject falls asleep or appears to be answering randomly)
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- The 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***
OHRP's "Informed Consent Checklist" can be found at
http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm

6.3 Waiving or Modifying Informed Consent

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

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

Please note that under most circumstances, loss of confidentiality is considered more than minimal risk. Risk also varies with the type of information being collected and how easily the subject can be identified based on data collected.

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 informed consent process. Investigators may not make this decision.

➢ ***Take Home Point***
The IRB can waive or alter the informed consent requirements in certain limited circumstances. The investigator is not authorized to make this decision without IRB approval.

➢ ***Related Internet Link***
45 CFR 46.116, "General requirements for informed consent" –
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116

6.4 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, and the subject's wishes will govern.
- 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***
  45 CFR 46.117, "Documentation of informed consent" – http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.117

6.5 Research in Different Cultures or Countries

The policy and methods for ensuring that prospective research subjects make an informed choice before taking part in research are consistent with the dominant Western conception of human autonomy, in particular the assumption that each individual should be allowed to make her or his own decisions.

The individualistic model is not universally applicable – not even within the borders of the United States, which hosts numerous distinct cultures or sub-cultures. Some cultural groups find different approaches to obtaining consent to take part in research more respectful. For example:

- It may be more appropriate to obtain permission from the entire community, or its representatives, before asking any individual to take part in research.
- In some areas the male head of household must be asked for permission for women or children in the household to take part in research.
- Providing a printed consent document obviously makes little sense in a non-literate society, and in some places – including many parts of the former Soviet Union – asking for a signature on a document will raise suspicions and unease among the populace.

The regulations and policies governing human subjects research are intended to promote high ethical standards and to protect human subjects from exploitation and harm, not to insult them or create unnecessary and meaningless obstacles to research. In cases like those outlined above, IRBs have a good deal of latitude in working with researchers to find innovative methods for protecting human subjects.

Researchers must plan ahead and anticipate cultural differences before going to the field. It is imperative that researchers working in different cultures or countries address that society's norms and standards in research plans and IRB applications before the research begins.

- ***Take Home Point***
  If typical policies and procedures for protecting human subjects do not make sense in a particular setting, researchers can make a case to the IRB for appropriate modifications.

- ***Related Internet Links***
  45 CFR 46.101, "To what does this policy apply?" - Sections g and h concern research in foreign countries – http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.101

The IRB Guidebook, Chapter 5, Section A, "Fieldwork" – http://www.hhs.gov/ohrp/irb/irb_chapter5.htm#h4

The IRB Guidebook, Chapter 6, Section K, "International Research" http://www.hhs.gov/ohrp/irb/irb_chapter6ii.htm#g12

6.6 Deception in Research

Some kinds of research seem to be impossible to conduct if the subject knows the purpose of the study. For example, it can be argued that responses to an interview would be hopelessly compromised if the subjects knew that the study was intended to uncover racist attitudes: Subjects would be likely to censor their responses in an effort to provide answers that they think the researcher would find acceptable.

The principle of respect for persons is important enough that all studies involving deception are scrutinized closely. Sometimes clever study designs can eliminate the need for deception. When no alternative can be found, however, a few tactics can be used to honor the principle of respect for persons. For example:

- The informed consent document can describe the goal in general or neutral terms. To continue the example mentioned above, it might work to describe the study as involving "group attitudes."
- If using general or neutral terms will not work, the informed consent document can make it clear that the purpose will be revealed after the subject has participated (e.g., at the end of the interview).

By using these tactics, the researcher can replace deception to some degree with ignorance; the second tactic even makes it clear that the subject is agreeing to remain ignorant on some aspect of the study. Even so, if either of these tactics are used, the researcher should fully inform each subject about the purpose of the research after the subject's data has been collected. The researcher should also be prepared to deal with any negative reactions the subjects might have to being deceived – all concerns and discomfort expressed by subjects should be resolved. This process is called "debriefing."

Some studies require deception about procedures. Continuing the same example, suppose that after going over the informed consent document, the researcher leaves the room for a moment on some pretext. While the subject waits, the researcher makes racist comments that the subject "accidentally" overhears.

Manipulating the subject in this way is more serious than keeping her or him in relative ignorance, and is more likely to be upsetting to the subject. Nevertheless, the subject should be debriefed after data collection.

➢ ***Take Home Point***
The use of deception in research is always a serious matter. Deception should be used only when absolutely necessary, and the researcher should always take appropriate steps to remediate the departure from a proper respect for persons.

➢ ***Related Internet Links***
Deception in research – http://www.research.indiana.edu/rschcomp/informed.html#deception

The IRB Guidebook, Chapter 5, Section A, "Behavioral Research" – http://www.hhs.gov/ohrp/irb/irb_chapter5.htm#h3

7 Special Protections for Vulnerable Populations

The Federal regulations provide for special protections for four categories of vulnerable populations:

- Pregnant women, fetuses, and neonates
- Prisoners
- Children
- Cognitively impaired individuals

Pregnant women, fetuses, and neonates are considered vulnerable primarily because of the special health issues associated with pregnancy and the physical frailty of the unborn and newly-born. Since risks to health do not feature strongly in non-biomedical research, this tutorial will say no more about pregnant women, fetuses, and neonates; if these categories of vulnerable populations are relevant to your research, you should seek additional guidance.

Prisoners, children, and cognitively impaired individuals are considered vulnerable because, as the Belmont Report puts it, they have "diminished autonomy" – that is, their ability to make informed and free decisions about their own lives is compromised because of their mental or moral abilities or, in the case of prisoners and other institutionalized people (including hospital patients and foster children), their dependant status.

In some cases, state and local laws will also be relevant in these considerations.

Researchers should be aware that the considerations covered in this section apply in principle to any potential subject who fits the relevant criteria even if he or she is not technically a member of the named vulnerable population. For example, a researcher who studies his or her own students (including students over 18 years of age) should be aware that such research carries risk of coercion similar to that in research with prisoners: Since the student-subjects are under the authority of the researcher, they have diminished autonomy and should be treated with care. Similar considerations apply whenever the subject is in a dependent relationship to the researcher, including, for example, when a nurse studies his or her own patients.

➢ ***Take Home Point***
Some populations of potential 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 Links***
45 CFR 46, Subpart B, "Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research" – http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartb

45 CFR 46, Subpart C, "Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects" – http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc

45 CFR 46, Subpart D, "Additional DHHS Protections for Children Involved as Subjects in Research" – http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd

The IRB Guidebook, Chapter 6, "Special Classes of Subjects" – http://www.hhs.gov/ohrp/irb/irb_chapter6.htm

7.1 Prisoners

➢ ***Definition***

"Prisoner means 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."
45 CFR 46.303(c)

It is important to note that special protections afforded to prisoners are also extended to research subjects who become a prisoners after the research has commenced. In some cases, such subjects must be dropped from a study.

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 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 to the subjects;
- Research on conditions particularly affecting prisoners as a class (for example, research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults); or
- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.

Research in the third and fourth categories have additional restrictions; for details, see the Related Internet Links at the end of this section.

Coercion is 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.

➢ ***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***
The IRB Guidebook, Chapter 6, Section E, "Prisoners"
http://www.hhs.gov/ohrp/irb/irb_chapter6ii.htm#g6

45 CFR 46, Subpart C, "Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects" –
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc

7.2 Children

➢ ***Definition***
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.

➢ ***Definition***
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, intellectual, and legal capacities are limited, making special considerations 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 the following four categories:

- Research not involving greater than minimal risk;
- Research involving greater than minimal risk, but presenting the prospect of direct benefit to the subject;
- 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; or
- 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 HHS 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.

Most research in one or more of the categories of exempt research (see Section 5.3.1 Exempt Review) is also exempt from continuing review when children are used as research subjects. The exceptions are research involving interview, surveys, and participant observation, which require expedited or full review (see Sections 5.3.2 Expedited Review and 5.3.3 Full Review).

As a general rule, in research with children, written parental permission is required. Permission from parents is usually indicated in a form similar to an informed consent document, constructed to request "your child" to participate.

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, such as 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 some cases, such as research on child abuse or venereal disease, parental permission may not be appropriate and 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.

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 manner that the child can reasonably be expected to understand (e.g., it is appropriate to the child's age, experience, maturity, etc.). 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 can overrule a child's decision **not** to participate in research **only** if the research is expected be therapeutic for the child.

- ***Take Home Point***
  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. Research involving children requires that the IRB make a determination about the particular category of research in which it belongs, and children should be given the opportunity to assent to their participation as they are able.

- ***Related Internet Links***
  The IRB Guidebook, Chapter 6, Section I, "Minorities" – http://www.hhs.gov/ohrp/irb/irb_chapter6ii.htm#g10

  45 CFR 46, Subpart D, "Additional DHHS Protections for Children Involved in Research" – http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd

7.3 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,

terminally ill patients, and persons with severely disabling physical handicaps may also be compromised in their ability to make decisions in their best interests.

The major ethical concern in research involving cognitively impaired persons is that their capacity to understand the nature of the research in which they have been asked to participate, their ability to make a reasoned and voluntary decision about participation, or both, may be compromised. This concern is compounded for individuals with such disabilities who are residents of institutions responsible for their total care and treatment; such a state of dependency may tend to make them more vulnerable to coercion – for example, a habit of compliance with routine care may incline them to volunteer as a research subject without adequate consideration, or a fear of being denied services may render them hesitant to decline to volunteer.

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

- Do such individuals comprise the only appropriate subject population? If the research questions focus on issues unrelated to their disorders or institutionalization, it may be inappropriate to enroll them as research subjects.
- Are there sufficient protections for privacy and confidentiality of information gathered?
- Have issues of consent and competence been adequately addressed? As a general rule, there should be specific evidence of each individual's capacity to understand and to make a choice before he or she is deemed unable to consent. When an individual is 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 his or her behalf. IRBs should also consider the possibility of obtaining assent (see the discussion on involving children in research on page 28) from potential research participants who are cognitively impaired.

➢ ***Take Home Point***
Cognitively impaired persons are those whose cognitive or emotional functions are diminished such that their 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 Link***
The IRB Guidebook, Chapter 6, Section D, "Cognitively Impaired Persons" – http://www.hhs.gov/ohrp/irb/irb_chapter6.htm#g5

8 After Initial Review

A researcher's relationship with the IRB does not end when her or his protocol has been approved; rather, it continues until the research project is completed. There are three circumstances when researchers must communicate with the IRB.

- If the PI wishes to modify any aspect of the approved research protocol, he or she must submit an amendment to the IRB.
- The PI must complete and submit to the IRB a continuing review form at least annually.

- When certain unanticipated problems arise, including protocol deviations and some problems that harm subjects, the PI must report the event to the IRB.

Amendments, continuing review, and reporting unanticipated problems are discussed in the following sections.

8.1 Amendments

Researchers must adhere to an approved protocol exactly. If the PI or sponsor wishes to change the protocol, even slightly, the PI must first secure approval from the IRB by submitting an amendment form.

All changes to a protocol are subject to review – changing the wording of recruitment advertisements, eliminating a procedure, adding questions to a survey, modifying subject inclusion or exclusion criteria, increasing or decreasing the number of subjects to be enrolled, adding a new researcher to the research team, etc. It is up to the IRB, not the PI, to judge whether a change is acceptable.

Depending on the nature of the change(s) and the policies of the responsible IRB, amendments can be subject to either expedited review or review by the full committee. Expedited review is typically conducted as often as once a week, but in most cases the full committee meets only once a month.

The change(s) must not be implemented until the PI receives notification of IRB approval of the amendment.

➢ ***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. Proposed changes may not be implemented until IRB approval has been granted.

➢ ***Related Internet Links***
Research at Indiana University – Research Compliance – Protection of Human Subjects – http://www.research.indiana.edu/rschcomp/human.html

8.2 Continuing Reviews

The nature of research dictates that outcomes can never be perfectly predicted. Since this is true not only of research findings, but also of risks and benefits, the actual risk/benefit ratio of a study can only be evaluated after research has begun. Thus IRB approval must be a continuing process, and when a research project receives initial approval the IRB determines how often the project should be re-evaluated, as well as the date for the next review. According to federal regulations, all research with human subjects must be reviewed at least annually. Each of these subsequent reviews is referred to as a "continuing review."

The IRB will notify the PI when it is time to submit a completed continuing review form, which must be completed even if the study was never initiated or was terminated for any reason.

If a PI leaves the university, 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 unanticipated problems that may affect the risk/benefit ratio. If necessary, the IRB can require revisions to the informed consent document or to study procedures, or termination of the research.

Continuing review is usually undertaken at the same level as the initial review (expedited or full). However, the level of review can be changed as appropriate in accord with changes in the risk assessment or other factors.

PIs also use continuing review to notify the IRB that a study is being closed or has been completed. When a study is closed or completed at any time other than at its continuing review, the PI should call the IRB and request a continuing review form.

- ***Take Home Point***
  IRB approval is an ongoing process and IRBs must review human subjects research at least once a year. If necessary, after continuing review the IRB can require changes to the research, including termination.

- ***Related Internet Links***
  Research at Indiana University – Research Compliance – Protection of Human Subjects – http://www.research.indiana.edu/rschcomp/human.html

8.3 Reporting Unanticipated Problems

Even the greatest care in designing and executing research cannot guarantee that no unwelcome events will occur. When something goes wrong, researchers are required to respond appropriately, which sometimes includes reporting the event to the IRB.

Instances in which the PI is responsible for promptly reporting the event to the IRB include:

- all unanticipated problems involving risks to subjects;
- some types of protocol deviations or violations (see Section 5.5 Responsibilities of All Researchers);
- any complaint of a subject that indicates unexpected risks and that cannot be resolved by the research team; and
- noncompliance (see Sections 5.5 Responsibilities of All Researchers and 5.6 Responsibilities of the Principal Investigator).

- ***Definition***
  Unanticipated problems involving risks to subjects are events which, in the opinion of the PI, caused harm to one or more subjects or others, or placed one or more subjects or others at increased risk of harm; and was unexpected; and was related to the research procedures.

Upon receipt of a report of an unanticipated problem, the IRB may require the PI to update the risk information in the informed consent document; suspend the study until it is assured that continuing the research will not jeopardize future subjects; or take other appropriate actions.

- ***Take Home Point***
  The reporting requirements for unanticipated problems depend on a variety of factors. The IRB may require changes to the consent form or the protocol or take other actions in response to an unanticipated problem.

- ***Related Internet Links***
  IUPUI – SOP for Unanticipated Problems Involving Risks to Subjects or Others and Noncompliance – http://www.iupui.edu/~respoly/human-sop/human-sop-index.htm

  IUB – Adverse Event policy – http://www.research.indiana.edu/rschcomp/operate.html#adverse

  Research at Indiana University – Research Compliance – Protection of Human Subjects – http://www.research.indiana.edu/rschcomp/human.html

9 Conclusion

Performing research using human subjects is a privilege, not a right, and it carries ethical and legal responsibilities. Indiana University is justly proud of its reputation as a major research institution, a reputation it owes to the intelligence, creativity, and diligence of its researchers, as well as to the institutional infrastructure that makes their success possible. The many systems of research oversight, including the Institutional Review Board, are intended to facilitate research and protect the integrity of research. This tutorial has briefly reviewed the need for formal mechanisms for protecting human subjects and the outlines of those mechanisms.

10 Useful Internet Links

- Belmont Report – http://www.hhs.gov/ohrp//humansubjects/guidance/belmont.htm
- Common Rule (45 CFR 46) – http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
- IRB Guidebook – http://www.hhs.gov/ohrp/irb/irb_guidebook.htm
- Office for Human Research Protections (OHRP) – http://www.hhs.gov/ohrp/
- Research at Indiana University – Research Compliance – Protection of Human Subjects – http://www.research.indiana.edu/rschcomp/human.html