Protecting Human Research Participants

NIH Office of Extramural Research

Introduction

Research with human subjects can occasionally result in a dilemma for ***investigators***. When the goals of the research are designed to make major contributions to a field, such as improving the understanding of a disease process or determining the efficacy of an intervention, investigators may perceive the outcomes of their studies to be more important than providing protections for individual participants in the research.

Although it is understandable to focus on goals, our society values the rights and welfare of individuals. **It is not considered ethical behavior to use individuals solely as means to an end.**

The importance of demonstrating respect for research participants is reflected in the principles used to define ethical research and the regulations, policies, and guidance that describe the implementation of those principles.

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Introduction

Who?

This course is intended for use by individuals involved in the design and/or conduct of **National Institutes of Health** (NIH) – funded human subjects research.

What?

This course is designed to prepare ***investigators*** involved in the design and/or conduct of research involving human subjects to understand their obligations to protect the rights and welfare of subjects in research. The course material presents basic concepts, principles, and issues related to the protection of research participants.

Why?

As a part of NIH's commitment to the protection of human subjects and its response to Federal mandates for increased emphasis on protection for human subjects in research, the NIH Office of Extramural Research released a policy on **Required Education in the Protection of Human Research Participants** in June 2000. This course is specifically designed for extramural investigators and is one (of many) possibilities for meeting the policy requirement.

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Introduction

Because this course is intended to allow ***investigators*** to fulfill the Required Education in the Protection of Human Research Subjects, it assumes that the investigators' research will be funded by NIH and is therefore subject to all **U.S. Department of Health and Human Services (HHS)** regulatory and NIH policy requirements.

The information presented is neither prescriptive nor exhaustive and does not replace or supersede local, state, or Federal regulations applicable to human research or any institutional policies regarding the protection of human subjects.

Course Objectives

Upon completion of this course, you should be able to:

- Describe the history and importance of human subjects protections
- Identify research activities that involve human subjects
- Discover the risks a research project might pose to participants
- Understand how to minimize the risks posed by a research project
- Describe additional protections needed for vulnerable populations
- Understand additional issues that should be considered for international research
- Describe appropriate procedures for recruiting research participants and obtaining ***informed consent***
- Identify the different committees that monitor human subjects protections
- Understand the importance of study design in the protection of research participants

The first module examines significant historical events that have contributed to the way we view the protections for participants in clinical research today.

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History

What This Module Covers:

Before discussing the current system for the protection of human subjects in research, it is important to review some of the significant historical events that have influenced current ethical guidelines and HHS regulations.

This module covers the following topics:

- Goals and Principles of Human Subjects Protection
- Nazi Medical War Crimes
- Syphilis Study at Tuskegee
- Timeline of Important Historical Events

Goals and Principles of Human Subjects Protection

Human subjects are essential to the conduct of research intended to improve human health. As such, the relationship between ***investigators*** and human subjects is critical and should be based on **honesty**, **trust**, and **respect**.

Historical Events

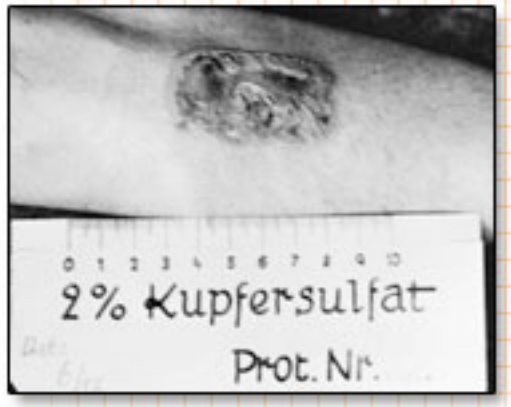
Nazi Medical War Crimes (1939–1945)

Although not the first example of harmful research on unwilling human subjects, the experiments conducted by Nazi physicians during World War II were unprecedented in their scope and the degree of harm and suffering to which human beings were subjected.

"Medical experiments" were performed on thousands of concentration camp prisoners and included deadly studies and tortures such as injecting people with gasoline and live viruses, immersing people in ice water, and forcing people to ingest poisons.

In December 1946, the War Crimes Tribunal at Nuremberg indicted 20 physicians and 3 administrators for their willing participation in the systematic torture, mutilation, and killing of prisoners in experiments. The Nuremberg Military Tribunals found that the defendants had:

- Corrupted the ethics of the medical and scientific professions
- Repeatedly and deliberately violated the rights of the subjects



This photograph documented the results of a medical experiment that included skin burns caused by doctors at the Ravensbrueck concentration camp in 1943. It was entered into evidence at the Doctors Trial at Nuremberg.

Photo source: Photo Archive, United States Holocaust Memorial Museum, courtesy of National Archives and Records Administration, College Park; used with permission.

The actions of these defendants were condemned as crimes against humanity. Sixteen of the twenty-three physicians/administrators were found guilty and imprisoned, and seven were sentenced to death.

Historical Events

The Nuremburg Code

In the August 1947 verdict, the judges included a section called **Permissible Medical Experiments**. This section became known as the **Nuremberg Code** and was the first international code of research ethics.

This set of directives established the basic principles that must be observed in order to satisfy moral, ethical, and legal concepts in the conduct of human subject research. The Code has been the model for many professional and governmental codes since the 1950s and has, in effect, served as the first international standard for the conduct of research.

View from above of the defendants dock during a session of the Medical Case (Doctors) Trial in Nuremberg, which ran from December 9, 1946 to July 19, 1947.

Photo source: Photo Archive, United States Holocaust Memorial Museum, courtesy of Hedwig Wachenheimer Epstein; used with permission.

The Code provides ten Directives for Human Experimentation

1. Voluntary consent of the human subject is absolutely essential
2. The experiment must yield generalizable knowledge that could not be obtained in any other way and is not random and unnecessary in nature
3. Animal experimentation should precede human experimentation
4. All unnecessary physical and mental suffering and injury should be avoided
5. No experiment should be conducted if there is reason to believe that death or disabling injury will

occur

6. The degree of risk to subjects should never exceed the humanitarian importance of the problem
7. Risks to the subjects should be minimized through proper preparations
8. Experiments should only be conducted by scientifically qualified ***investigators***
9. Subjects should always be at liberty to withdraw from experiments
10. Investigators must be ready to end the experiment at any stage if there is cause to believe that continuing the experiment is likely to result in injury, disability or death to the subject

Historical Events

The Syphilis Study at Tuskegee

Arguably the most notorious example in the United States of the violation of the rights and welfare of human subjects was the long-term study of black males conducted by the United States Public Health Service in Tuskegee, Alabama. This study of the natural history of untreated syphilis was initiated in the 1930s and continued until 1972.

The Syphilis Study at Tuskegee involved approximately 600 African-American men: about 400 with syphilis (cases) and about 200 without syphilis (controls). These men were recruited without ***informed consent*** and, in fact, were led to believe that some of the procedures done in the interest of research (e.g., spinal taps) were actually "special free treatment."

An unidentified subject of the Tuskegee Syphilis Study provides a blood sample to study investigators in the early 1950s.

Photo source: Records of the Centers for Disease Control and Prevention.

By 1936, it was apparent that many more infected men than controls had developed complications, and 10 years later, reports indicated that the death rate among those with syphilis was about twice as high as it was among the controls. In the 1940s, penicillin was found to be effective in the treatment of syphilis. The Syphilis Study at Tuskegee continued, however, and the men were neither informed about nor treated with the antibiotic.

Historical Events

Outcomes of the Syphilis Study at Tuskegee

The first accounts of this study appeared in the national press in 1972. The resulting public outrage led to the appointment of an ad hoc advisory panel by the Department of Health, Education and Welfare (which later was split into the Department of Education and the Department of Health and Human Services [HHS]) to review the study and develop recommendations to ensure that such experiments would never again be conducted.

Outcomes included:

1. National Research Act of 1974
2. **HHS Policy for Protection of Human Subjects**
3. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Timeline of Events

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Protecting Human Research Participants

NIH Office of Extramural Research

Codes and Regulations

What This Module Covers:

- The Belmont Report – Ethical Principles and Guidelines for the Protection of Human Subjects of Research
- HHS Regulations for the Protection of Human Subjects, 45 CFR 46

The Objectives For This Module Are:

- To identify the three principles of ethical human subjects research identified in the Belmont Report
- To comprehend the current HHS regulations, including:
  - Risks associated with participation in research and appropriate protections against risks
  - Vulnerable populations that need specific protections
  - Situations in which research involving humans is exempt from regulatory requirements

The Belmont Report

Following the public outrage over the Syphilis Study at Tuskegee, Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974. The National Commission was charged with:

1. Identifying the ethical principles to guide all research involving human subjects
2. Developing guidelines for the conduct of ethical research involving human subjects

In 1979, the National Commission drafted **The Belmont Report – Ethical Principles and Guidelines for the Protection of Human Subjects of Research**.

The Belmont Report identified **three principles** essential to the ethical conduct of research with humans:

1. **Respect for persons**
2. **Beneficence**
3. **Justice**

These three basic principles serve as the foundation of the current HHS regulations and guidelines for the ethical conduct of human subjects research supported by HHS.

Respect for Persons

> To respect autonomy is to give weight to the autonomous person's considered opinions and choices while refraining from obstructing his or her actions...
>
> – Belmont Report

The principle of respect for persons can be broken down into two basic ideas:

1. Individuals should be treated as autonomous agents

An ***autonomous person*** is able to:

- Consider the potential harms and benefits of a situation
- Analyze how those risks and potential benefits relate to his or her personal goals and values
- Take action based on that analysis

Prospective research participants must be given the information they need to determine whether or not they want to participate in research. There should be no pressure to participate and ample time to decide. Respect for persons demands that participants enter into the research voluntarily and with adequate information. This is called ***informed consent***, and will be covered in detail in other sections of this training.

2. Persons with diminished autonomy are entitled to additional protections

According to the Belmont Report, “Special provisions may need to be made when an individual’s comprehension is severely limited or when a class of research participants is considered incapable of informed decision making (e.g. ***children***, people with severe developmental disorders, or individuals suffering from dementias). Even for these persons, however, respect for persons requires giving them the opportunity to choose, to the extent they are able, whether or not they wish to participate in research activities. In some cases, respect for persons may require seeking the ***permission*** of other parties, such as a parent or legal guardian.”

The challenges in applying the **Belmont principle of respect for persons** are in:

- Making sure that potential participants comprehend the risks and potential benefits of participating in research
- Avoiding influencing potential participants’ decisions either through explicit or implied threats (***coercion***) or through excessive ***compensation*** (***undue influence***)

Beneficence

> Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term beneficence is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation.
>
> – Belmont Report

Two general rules have been articulated as complementary expressions of beneficent actions:

1. Do no harm
2. Maximize possible benefits and minimize possible harms

The challenge inherent in applying the **Belmont principle of beneficence** is how to determine when potential benefits outweigh considerations of risks and vice versa.

Justice

> Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.
>
> – Belmont Report

Justice requires that individuals and groups be treated fairly and equitably in terms of bearing the burdens and receiving the benefits of research.

The principle of justice may arise in decisions about inclusion and exclusion criteria for participation in research and requires ***investigators*** to question whether groups are considered for inclusion simply because of their availability, their compromised position, or their vulnerability — rather than for reasons directly related to the problem being studied.

The challenge of applying the **Belmont principle of justice** is how to decide which criteria should be used to ensure that harms and benefits of research are equitably distributed to individuals and populations.

Review

The Belmont Report identifies three principles essential to the ethical conduct of research with humans.

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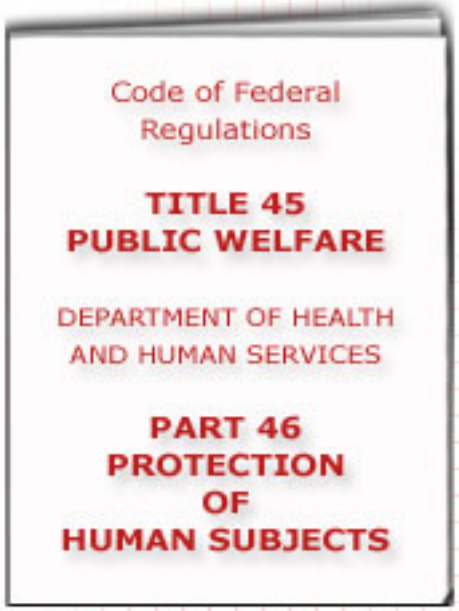
The HHS Regulations – Protection of Human Subjects



The ethical principles for research involving human subjects described in the Belmont Report are codified in the Code of Federal Regulations, **45 CFR 46**. The NIH follows all Subparts of the HHS regulations:

Subpart A – Basic HHS Policy for Protection of Human Research Subjects

Subpart B – Additional Protections for ***Pregnant*** Women, Human ***Fetuses*** and ***Neonates*** Involved in Research

Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving ***Prisoners*** as Subjects

Subpart D – Additional Protections for Children Involved as Subjects in Research

Subpart A - Basic HHS Policy for Protection of Human Research Subjects

Subpart A, also called **"The Common Rule"**, describes the required protections for all human subjects.

Subpart A defines a ***human subject*** as "a living individual about whom an ***investigator***...conducting research obtains:

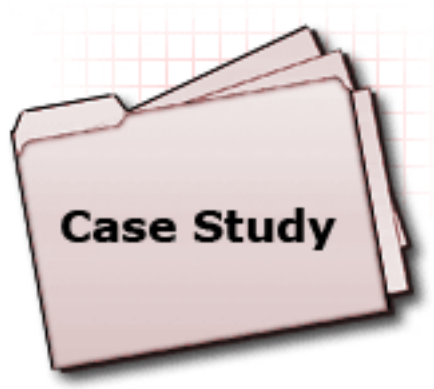
1. Data through intervention or interaction with the individual, or
2. Identifiable private information."

Subpart A defines ***research*** as "a systematic investigation...designed to develop or contribute to generalizable knowledge."

This definition includes:

- Research development
- Testing
- Evaluation

Case Study: Human Heart Study



An ***investigator*** will be using human hearts in order to study factors leading to heart failure. One group of normal, control hearts will be obtained from cadavers. A set of diseased hearts will be obtained from individuals who are to receive a heart transplant.

Does this study involve human subjects?

Yes, this study involves human subjects

Correct!

The use of healthy hearts from cadavers does not constitute human subjects research, because the individuals from whom the hearts will be obtained are not living, but the use of the diseased hearts removed during transplant surgery is human subjects research, since the donors are alive.

No, this study does not involve human subjects

The correct answer is Yes.

Additional Protections

The Belmont principle of respect for persons states, in part, that individuals with ***diminished autonomy*** may need additional protections. ***Subparts B, C, and D*** describe additional protections for some of the populations that are considered particularly vulnerable:

Subpart B
Additional Protections for ***Pregnant*** Women, Human ***Fetuses*** and ***Neonates*** Involved in Research

Subpart C
Additional Protections Pertaining to Biomedical and Behavioral Research Involving ***Prisoners*** as Subjects

Subpart D
Additional Protections for ***Children*** Involved as Subjects in Research

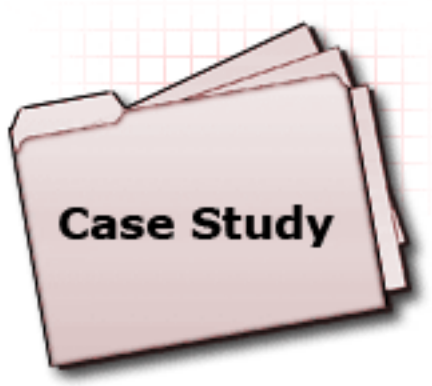
Vulnerable Populations

Subparts B, C and D define the specific categories of research in which ***pregnant women***, human ***fetuses*** and ***neonates***, ***prisoners***, or ***children*** respectively may be involved. The subparts describe additional requirements for ***informed consent***, and may specify additional responsibilities for the Institutional Review Board (IRB) when reviewing research involving these populations, and list the requirements for research that need additional levels of review and approval.

Other vulnerable populations include, but are not limited to, mentally disabled persons and economically and/or educationally disadvantaged persons. While the regulations do not specify what additional protections are necessary for these groups, the HHS regulations (**45 CFR 46.111**) do require that ***investigators*** include additional safeguards in the study to protect the rights and welfare of these individuals "when some or all of the subjects are likely to be vulnerable to ***coercion*** or ***undue influence***."

Case Study: Fetal Imaging

Indicate whether the HHS regulations require the ***investigator*** to provide additional protections for participants in the study under **Subparts B, C or D**:



A study proposes to test a novel fetal imaging technology designed to enhance image quality and allow physicians to assess more accurately prenatal health. This technology has been tested both on ***pregnant*** mammals and non-pregnant women with no adverse effects. Women will be recruited at their regularly scheduled prenatal check-ups and those who consent to participate will receive the experimental scan.

Does this study require the investigator to provide additional protections for participants?

Yes, the study involves a vulnerable population

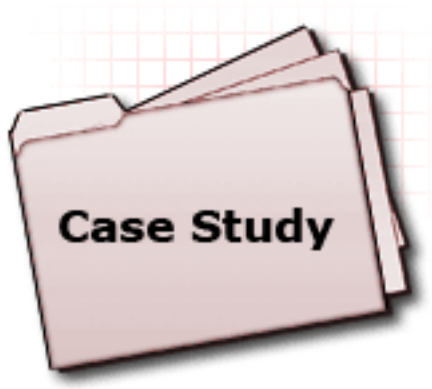
Correct!

This study involves a vulnerable population. Because the research will be conducted with pregnant women and fetuses, the requirements of ***Subpart B*** apply.

No, the study does not involve a vulnerable population

The correct answer is Yes.

Case Study: Observational Study of Challenges Returning to Work



Indicate whether the HHS regulations require the following studies to provide additional protections for the study's subject populations under **Subparts B, C or D**:

A study proposes to observe the challenges for former ***prisoners*** returning to office jobs. Researchers will recruit individuals who have spent over ten years in prison, have completed their sentences, and are now interviewing for office jobs.

Does this study requires additional protection for the subject population?

Yes, the study involves a vulnerable population

The correct answer is No.

This study does not involve a vulnerable population. The participants in this research are not considered prisoners, per ***Subpart C***, because they have completed their period of involuntary confinement and are no longer "**confined or detained in a penal institution**" nor are they "detained pending arraignment,

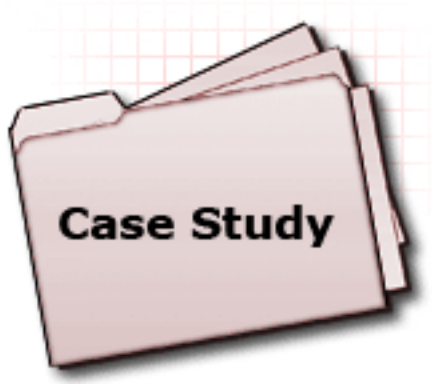
trial, or sentencing."

No, the study does not involve a vulnerable population

Correct!

This study does not involve a vulnerable population. The participants in this research are not considered prisoners, per ***Subpart C***, because they have completed their period of involuntary confinement and are no longer "**confined or detained in a penal institution**" nor are they "detained pending arraignment, trial, or sentencing."

Case Study: Treatment and Prevention Research in Adolescents



Indicate whether the HHS regulations require the following studies to provide additional protections for the study's subject populations under **Subparts B, C or D**:

A study proposes to examine the effectiveness of a medical treatment and prevention program for adolescents in a location where the legal age for consent to such treatment is 12. The adolescents involved range from ages 12 to 17.

Does this study require additional protections be provided for the subject population?

Yes, the study involves a vulnerable population

The correct answer is No.

The regulatory definition of children depends both on the local laws and on the specific treatments or procedures that will be involved in the research. Because the location in which the research will be conducted allows 12-year-olds to consent to the treatment, the participants in this research are not considered children under the HHS regulations and can provide informed consent to participate in the study. While the regulations do not require the additional protections of ***Subpart D*** for children in this

study, the IRB may require some additional protections if they feel that the adolescents who will be involved in the study are vulnerable.

No, the study does not involve a vulnerable population

Correct!

The regulatory definition of children depends both on the local laws and on the specific treatments or procedures that will be involved in the research. Because the location in which the research will be conducted allows 12-year-olds to consent to the treatment, the participants in this research are not considered children under the HHS regulations and can provide informed consent to participate in the study. While the regulations do not require the additional protections of ***Subpart D*** for children in this study, the IRB may require some additional protections if they feel that the adolescents who will be involved in the study are vulnerable.

Requirements for Federal Support of Human Subjects Research

The HHS regulations (**45 CFR 46.120**) require that Federal Departments and Agencies that conduct or support human subjects research must evaluate all applications for research using the following criteria:

- Risks to the subjects
- Adequacy of protection against these risks
- Potential benefits of the research to the subjects and others
- Importance of the knowledge gained or to be gained

Equivalent Protections for International Research

When research covered by the HHS regulations takes place in countries other than the United States, the HHS regulations (**45 CFR 46.101(h)**) allow a Department or Agency head to approve the substitution of alternative polices, codes, or regulations to protect human subjects in lieu of the requirements of 45 CFR 46 as long as the alternatives afford protections that are at least equivalent to those provided in 45 CFR 46.

In a **Federal Register Notice** on July 7, 2006, HHS clarified that the requirements of the HHS regulations (45 CFR 46) must be satisfied for all HHS-conducted or -supported research covered by the **Federalwide Assurance**, regardless of whether the research is conducted domestically or internationally. As of the publication of that Notice, HHS had not deemed any other procedural standards equivalent to 45 CFR 46.

Engagement in Human Subjects Research

Each institution that is engaged in NIH-funded human subjects research must:

- Obtain or hold a current **Federalwide Assurance** (FWA), assuring that an institution will comply with HHS regulatory requirements for the protection of human subjects (this is obtained from the HHS Office for Human Subjects Protections (OHRP); and
- Certify to NIH that grant applications and contract proposals describing research involving human subjects has been reviewed and approved by an Institutional Review Board (IRB) designated in the FWA, and will be subject to continuing review by an IRB.

IRBs are committees that consist of 5 or more members with varying expertise and diversity that are responsible for reviewing and approving human subjects research activities on behalf of institutions.

The Common Rule specifies:

- IRB membership (**45 CFR 46.107**)
- IRB functions & operations (**45 CFR 46.108**)
- IRB review of research (**45 CFR 46.109** and **45 CFR 46.110**)
- Criteria for IRB approval of research (**45 CFR 46.111**)

And more!

The roles and responsibilities of IRBs are discussed extensively in the module on **Beneficence**.

Exemptions

The HHS regulations describe categories of human subjects research that may be exempt from requirements described in the HHS regulations including IRB oversight.

Studies proposing only research that falls under one or more of the exempt categories of research do not require IRB review and approval, but the HHS Office for Human Research Protections (OHRP) has stated that: "**Institutions should have a clear policy in place on who shall determine what research is exempt under 46.101(b)**" and that ***investigators*** should not be able to determine whether or not their own research is exempt. This authority should rest with the IRB or other entity designated by the institution.

The exemptions can be found at **45 CFR 46.101(b)**.

Codes and Regulations: Summary

This module examined:

- The three basic ethical principles described in the Belmont Report
- The subsequent codification of these principles in 45 CFR 46 of the Code of Federal Regulations

The Belmont Report summarizes the three basic ethical principles of clinical research as:

1. Respect for persons
   - Individuals should be treated as ***autonomous agents***
   - Persons with ***diminished autonomy*** are entitled to additional protections

2. Beneficence
   - Do no harm
   - Maximize possible benefits and minimize possible harms

3. Justice
   - Requires that individuals and groups be treated fairly and equitably in terms of bearing the burdens and receiving the benefits of research

45 CFR 46 codifies these basic principles:

- Subpart A describes the required protections for all Federally conducted or supported human subjects research
- Subpart B covers additional protections for pregnant women, human ***fetuses*** and ***neonates***
- Subpart C outlines additional protections pertaining to biomedical and behavioral research involving ***prisoners*** as subjects
- Subpart D provides for additional protections for ***children***

Additionally, the regulations discuss methods of determining whether research is exempt from the regulations.

Protecting Human Research Participants

NIH Office of Extramural Research

Respect for Persons

What This Module Covers:

- The ***informed consent*** process
- Requirements for documentation of informed consent
- Waivers of informed consent
- ***Diminished autonomy*** and ***legally authorized representatives***
- Participation of ***pregnant women*** in research
- ***Assent*** from ***children*** and ***permission*** from parents
- Obtaining informed consent from ***prisoners***
- Community consent

The Objectives For This Module Are:

- To outline the requirements for informed consent
- To state when waivers of informed consent and legally authorized representatives are appropriate

Respect for Persons

> To respect autonomy is to give weight to the autonomous person's considered opinions and choices while refraining from obstructing his or her actions...
>
> – Belmont Report

The principle of respect for persons can be broken down into two basic ideas:

1. Individuals should be treated as ***autonomous agents***
2. Persons with ***diminished autonomy*** are entitled to additional protections

Informed Consent

The Belmont principle of respect for persons is primarily applied by requiring that all human subjects research participants provide voluntary ***informed consent*** to participate in research.

The three fundamental aspects of informed consent are:

Voluntariness

Individuals' decisions about participation in research should not be influenced by anyone involved in conducting the research: "...consent must be freely given or truly voluntary." [1]

Comprehension

Individuals must have the mental or decisional capacity to understand the information presented to them in order to make an informed decision about participation in research.

Disclosure

HHS regulations (**45 CFR 46.116(a)**) require that researchers disclose:

1. The purpose of the study
2. Any reasonably foreseeable risks to the individual

3. Potential benefits to the individual or others
4. Alternatives to the research protocol
5. The extent of confidentiality protections for the individual
6. ***Compensation*** in case of injury due to the protocol
7. Contact information for questions regarding the study, participants' rights, and in case of injury
8. The conditions of participation, including right to refuse or withdraw without penalty

This disclosure must be made in such a way that it provides a ***reasonable person*** the information she or he would need in order to make an informed decision.

Informed Consent

The HHS regulations (45 CFR 46.116) require that ***investigators*** obtain legally effective ***informed consent*** from prospective participants in a way that allows them to consider whether or not to participate and that minimizes the possibility for ***coercion*** or ***undue influence*** .

Potential participants must understand that enrolling in the research is voluntary and that they may withdraw from the study at any time without penalty or loss of benefits (45 CFR 46.116(a)).

In order for participation in research to be voluntary, the potential for coercion and undue influence must be minimized.

Case Study: Sleeping Sickness Study on Campus

An ***investigator***, who is a professor at a large university, is developing a grant application for submission to the NIH to study sleeping sickness (trypanosomiasis). This study will investigate surface antigen expression in trypanosomes, the parasite that causes sleeping sickness, in order to develop a vaccine. These parasites grow in human blood and lymph.

The study will require fresh human blood daily for several months, and thus will require research participants. A research assistant will maintain a schedule of research participants to ensure that the study performs one collection per day and that blood collections are in accordance with **American Red Cross Blood Donation Eligibility Guidelines**, i.e., healthy, weigh at least 110 pounds, and have not donated a pint (570 ml.) of whole blood in the last 8 weeks (56 days). Participants will be compensated.

It is now time to make a decision about ***recruitment*** of the research participants.

Case Study: Sleeping Sickness Study on Campus

Based on the number of students and employees in her classes and lab, the researcher feels confident that she will have enough participants needed for the proposed research if she simply recruits among them. But she knows that some colleagues advertise their studies through postings on campus. The ***investigator*** is faced with two possible options for recruiting normal, healthy research participants:

Recruit the students in her upper level classes and the technicians from her lab, and give $5 ***compensation*** to participants per blood draw, or

Recruit from the general university population (students, faculty and staff) by posting fliers around campus, and give $5 compensation to participants per blood draw

The investigator discusses the grant application and proposed research procedures with you. You think that the compensation plan is appropriate and that $5 would not be an ***undue influence*** for either population to participate.

From which population would you advise the researcher to recruit?

Recruit the students in her upper level classes and the technicians from her lab to participate in the study

The correct answer is to recruit from the campus population.

Asking for study participants from a population over which a researcher has authority is not the best idea.

It is generally agreed that students and employees are groups that can be vulnerable to coercion.

Even though the researcher may feel confident that she would never let her students' and employees' decisions about participation affect her opinions about them, her students and employees might feel pressured to participate simply because she is in a position of authority.

Post fliers around campus to recruit participants from the campus population (students, faculty and staff)

Correct!

Recruiting for the study participants from the students, faculty and staff of the university is the best choice.

It is generally agreed that students and employees are a group that can be vulnerable to coercion.

However, in this situation, the recruitment plans include the entire campus community.

As long as she does not mention her proposed research in her classes and there is no indication that she will be in a position of authority over the individuals who choose to contact her, the proposed population is not vulnerable to coercion.

Informed Consent

Informed consent should be understood as an **on-going process** rather than a level of legal protection for an institution. It is not intended to be a one-time act of having a participant sign a form.

Informed consent is designed to inform research subjects about the purpose, risks, potential benefits and alternatives to the research that allows people to make a decision about whether or not to participate based on their own goals and values. This exchange of such information should occur at enrollment and throughout the study.

Informed Consent

Investigators are responsible for providing information during the ***informed consent*** process in a manner that is understandable to the potential participants. ***Investigators*** should not enroll anyone in a study unless the investigator is confident that the individual comprehends all information disclosed and agrees to procedures described during the informed consent process.

Investigators can use methods in addition to a **consent form** to enhance individuals' comprehension. Some examples include:

- Oral presentations that provide potential participants with the opportunity to discuss the information and ask questions
- Providing additional educational materials, such as brochures, about research in general and/or the specific procedures that will be used in the study
- Video presentations that familiarize potential participants with the procedures that will be used in the study

The informed consent process must be delivered in "… **language that is understandable to the subject** …" (45 CFR 46.116). This may mean adjusting the reading levels of documents provided or translating documents and presentations into the language with which participants are most comfortable.

Case Study: Sleeping Sickness Study on Campus

Now that your colleague studying sleeping sickness has decided on the method of recruitment for the study participants, she must write an ***informed consent*** document for the participants to sign.

The researcher has prepared two different draft consent documents and must select one to submit to her IRB for review.

Read the two consent documents and then choose the document that best informs the potential participants about the study in which they will enroll:

- Consent Document 1
- Consent Document 2

Which of these two consent documents would you choose to use?

Choose Consent Document 1

This would not be the best consent document to choose.

Consent Document 1 does not include all of the required elements of informed consent (**45 CFR 46.116**) and does not protect against the perception of coercion.

Although this consent form does include information regarding potential benefits to others and ***compensation*** for participants, there is no information regarding the following:

1. Risks for the participant
2. Confidentiality protections
3. Contact information for questions regarding the study
4. The conditions of participation, including right to refuse or withdraw without penalty

Consent Document 2 more thoroughly addresses all of the regulatory requirements for informed consent.

Choose Consent Document 2

Consent Document 2 is the best choice.

Consent Document 2 contains all of the required elements of informed consent (**45 CFR 46.116**) and protects against the perception of ***coercion*** by emphasizing the fact that participation is voluntary and explaining how someone can withdraw from the study if they wish.

Consent Document 2 includes the following required elements of informed consent:

1. The purpose of the study
2. Foreseeable risks/discomforts to the individual
3. Potential benefits to the individual or others
4. Confidentiality protections for the individual
5. Compensation plan
6. Contact information for questions regarding the study, participants' rights, and in case of injury
7. The conditions of participation, including right to refuse or withdraw without penalty

Respect for Persons

Consent Document 1

Surface Antigen Expression in Trypanosomes

Dr. X

You are invited to participate in this study by giving blood on a voluntary basis, but no more than five times in an eight week period. The research project is anticipated to continue for four years.

All blood draws will be performed by qualified technicians at the Medical Center Blood Bank. 100 ml of blood will be withdrawn from a vein in your arm.

Although you will not benefit directly from participating in this study, you will make a major contribution to the information known about trypanosomiasis, also known as sleeping sickness. In the future, others may benefit because scientists and doctors will learn about how parasites cause sleeping sickness, and will develop vaccines to prevent it.

You will be paid $5 for the time and travel required to give blood.

Your signature on this form means that you understand that participation is voluntary, and you may withdraw from the study at any time.

_____
Signature of Participant

Contact information for Dr. X:
Email: drx@university.edu
phone: 123-456-7890

Respect for Persons

Consent Document 2

Surface Antigen Expression in Trypanosomes

Dr. X

Dr. X's laboratory studies the parasite which causes trypanosomiasis, also known as sleeping sickness. This study will look at the effects of different surface antigens (proteins) produced by the parasites in human blood. The goal is to identify how different surface antigens are expressed by the parasites.

You are invited to participate in this study by giving blood on a voluntary basis, but no more than five times in an eight week period. The research project is anticipated to continue for four years.

All blood draws will be performed by qualified technicians at the Medical Center Blood Bank. 100 ml of blood will be withdrawn from a vein in your arm. None of the procedures are experimental.

During the collection of blood, you may experience discomfort and bruising at the site of collection. To minimize these risks, you will be asked to lie down while an experienced technician collects the blood sample. You may feel light-headed after having blood drawn. If you feel faint, you should not get up and should notify a nurse.

Although you will not benefit directly from participating in this study, you will make a major contribution to the information known about sleeping sickness. In the future, others may benefit because scientists and doctors will learn about how parasites cause sleeping sickness and will develop vaccines to prevent it.

A research assistant will keep a record of all blood draws in a secure database. Only the professional staff at the Medical Center will know the identity of study participants.

You will be paid $5 for the time and travel required to give blood. If you feel that you have been injured as a direct result of participating in the study, please contact Dr. X at 123-456-7890.

Your signature on this form means that you understand the information presented, and that you want to participate in the study. You understand that participation is voluntary, and you may withdraw from the study at any time.

_____
Signature of Participant

Contact information for Dr. X:
Email: drx@university.edu
phone: 123-456-7890

Close

Waivers of Informed Consent

The HHS regulations (**45 CFR 46.116(c)**) allow institutional review boards (IRBs) to waive or alter **some or all of the required elements of *informed consent***

if all of the following conditions are met:

1. "The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; (iv) possible changes in methods or levels of payments for benefits or services under those programs, and
2. The research could not practicably be carried out without the waiver or alteration."

Waivers of Informed Consent

The HHS regulations (**45 CFR 46.116(d)**) also allow IRBs to waive or alter some or all of the required elements of ***informed consent*** if all of the following conditions are met:

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

Practicability and Waivers of Informed Consent

Decisions about waivers of informed consent often concern the issue of **practicability**. Although practicability is not defined in the HHS regulations, it is not sufficient for an ***investigator*** to argue simply that seeking consent would be time-consuming or incur additional cost.

In some situations, a waiver of ***informed consent*** may be appropriate for a medical record review or for using existing data or specimens that can be linked to identifiable individuals. Specific decisions regarding practicability are made by the IRB.

Case Study: New Analyses of Existing Data

An ***investigator*** has collected identifiable data from participants in a research study. She has completed the analyses that were originally proposed and described in the NIH grant application, the protocol approved by the IRB, and the ***informed consent*** document approved by the IRB. The informed consent document made no mention of using the data in additional research but gives ***permission*** for the investigator to re-contact the participants.

Now, based on new hypotheses, the investigator plans to conduct new analyses to fulfill purposes different from those described in the informed consent document, the NIH grant application and the IRB-approved protocol. She knows that she needs to obtain approval for the new research from her IRB and her NIH Program Official.

Does the investigator need to obtain new informed consent from the participants?

Yes, the investigator does need to obtain new informed consent

You *may* be correct.

The investigator needs to obtain informed consent ***unless***:

- The criteria for a waiver are met, and
- The IRB has approved a waiver of informed consent.

No, the investigator does not need to obtain new informed consent

You *may* be correct.

The investigator does not need to obtain new informed consent ***as long as*** the IRB has approved a waiver of informed consent.

Requirements for Documentation of Informed Consent

The HHS regulations **require that *informed consent* be documented**

using a written form that either contains all of the required elements (**45 CFR 46.116(a)**) or a short form that states that all of the required elements have been presented orally. This form must be signed by either the participant or the participant's ***legally authorized representative*** (**45 CFR 46.117**).

The HHS regulations (**45 CFR 46.117(c)**) allow IRBs to waive the requirement for **documented** informed consent if they find that either:

1. "The only record linking the participant to the research would be the [informed] consent document and the principal risk to the participants would be the potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern, or
2. The research presents no more than ***minimal risk*** to the participants and involves no procedures for which written consent is normally required outside of the research context."

Diminished Autonomy

An individual's ***autonomy*** can be affected by several factors including age, cognitive impairment, illness, and treatments. An individual's capacity to consent to a particular study should be assessed based on:

1. The individual's level of capacity, and
2. The complexity and risks of the study, i.e., the capacity needed for an individual to be able to understand the study well enough to consent to participate

Decisional Capacity and Legally Authorized Representatives

The Belmont principle of respect for persons states that investigators need to make special provisions when including individuals in research who have diminished capacity for making decisions in their own best interests.

The HHS regulations, therefore, require that ***legally authorized representatives*** provide voluntary ***informed consent*** for individuals with diminished capacity to participate in research (**45 CFR 46.116**).

While the HHS regulations allow for legally authorized representatives to make substituted decisions for individuals who need assistance, ***investigators*** should obtain consent from the participants to the extent possible. Because some individuals may be only temporarily or intermittently incapacitated (e.g., due to injury or medications), investigators should attempt to approach these individuals at a time when they do have the capacity to consent to research. If a participant regains the capacity to consent to research after the research has begun, investigators should obtain the participant's informed consent before continuing his or her participation in the study.

Participation of Pregnant Women in Research

Because research involving ***pregnant women*** may affect the woman, the ***fetus***, or both the woman and the fetus, additional issues must be considered for studies of pregnant women.

The HHS regulations require:

- Preclinical studies be completed prior to the involvement of pregnant women
- A consideration of risks and potential benefits for the fetus and pregnant woman

The HHS regulations prohibit:

- Inducements of any kind to terminate a pregnancy
- ***Investigators*** from taking part in decisions about terminating a pregnancy
- Investigators from determining the viability of a ***neonate***

Investigators, IRBs, and funding agencies must comply with requirements described in Subpart B of the HHS regulations.

Children's Participation in Research

Children may not have full capacity to make decisions in their own best interests; and therefore:

- Children are considered a vulnerable population, and
- Children are unable to provide "legally effective ***informed consent***" as required by the HHS regulations at **45 CFR 46.116**

Because children cannot provide informed consent, children provide ***assent*** to participate in research, to the extent that they are able, and parents/guardians give ***permission*** for a child to participate in research.

The additional regulatory requirements of assent and permission for research involving children (**45 CFR 46.408**) are intended to make sure that ***investigators*** respect the decisions of both children and their parents. Parental permission must be obtained for research involving children "in accordance with and to the extent that consent is required by 45 CFR 46.116."

Assent and Permission for Children's Participation in Research

The ages, maturity and psychological states of the ***children*** involved in the research should be taken into account when determining whether children have the capacity to ***assent***. This determination is made by the IRB. The IRB may require that ***investigators*** conduct an individual assessment of each child's ability to assent or may make a general determination for all children involved in the study.

The content and language of the assent process should be appropriate to the age and education/developmental stage of the children providing assent. It may be necessary to have multiple assent documents or assent processes if the children to be enrolled in the research are of different ages or at different stages of development.

Protecting Human Research Participants

NIH Office of Extramural Research

Respect for Persons

Case Study: Lack of Assent from a Child

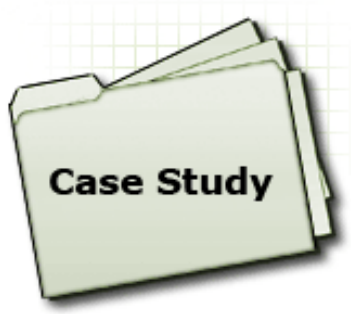
A 7-year-old ***child*** has a rare genetic disorder. No treatment is currently available. You have designed a longitudinal study that will examine the progression of the disorder. The study will involve standard physical and psychological examinations, including drawing 10ml of blood 4 times per year.

After enrollment, at which time the parents provided ***permission*** for the child to participate in the study and the child provided assent, he panics and screams that he doesn't want to participate and wants to go home when he sees the nurse holding a needle for the blood draw. The parents are present and want the child to participate.

Do you need to withdraw this child from your study because he has withdrawn his *assent*?

This is not an easy question because it does not have a clear "yes" or "no" answer. Various issues to consider are explored on the **next page**.

Case Study: Lack of Assent from a Child



A number of issues should be considered to assist with decision-making. First, ***investigators*** need to identify the institutional resources available to help decide the appropriate action, e.g. the IRB, the Ethics Committee, a research participant's advocate, the patient's personal physician. Second, the investigators and others involved in the deliberations should consider issues such as:

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Obtaining Informed Consent from Prisoners

Research involving ***prisoners*** requires approval by an IRB whose membership is specifically constituted to address the concerns of this vulnerable population per **45 CFR 46.304**. If the research is conducted or supported by HHS, it must also be approved by the Secretary of HHS through the Office for Human Research Protections (OHRP). This approval signifies that "**the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2)**."

The HHS regulations (**45 CFR 46, Subpart C**) require additional protections for prisoners who are involved as participants in research because they may "be under constraints as a result of their incarceration that could affect their ability to make a truly voluntary decision about whether or not to participate in research."

The requirements specific to ***informed consent*** for prisoners are:

1. "Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired"
2. "Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole"

Community Consultation

In some cultures it is not appropriate to obtain ***informed consent*** **solely** from the individual participants, because the individual's interests may be considered to be intimately entwined with their community's interests. The appropriate way to attain community consent may vary widely, but is often achieved through meetings with large groups of community representatives or community leaders.

It is also appropriate to consult a community before conducting research when the research involves risk to discrete, identifiable populations. For example, members of a community may feel stigmatized if a number of members of that community participate in research that may reveal unpopular or dangerous traits.

Emergency Research

One example of a situation in which community consent is required is emergency research in life-threatening situations where obtaining ***informed consent*** is not feasible. In order for ***investigators*** to obtain a waiver of informed consent for emergency research, investigators must obtain consent from the communities in which the research will be conducted in addition to a number of other requirements. These requirements are described in **Informed Consent Requirements in Emergency Research**.

Investigators should note that this **emergency waiver** of informed consent does not apply to research that falls under **Subpart B** (***pregnant*** women, human ***fetuses*** and ***neonates***) or **Subpart C** (***prisoners***) of the HHS regulations.

Respect for Persons: Summary

During the ***informed consent*** process, the principle of respect for persons is applied by requiring that all human subjects provide voluntary informed consent to participate in the research.

Practical application of this principle means that potential study participants must:

- Give their consent freely and voluntarily
- Have the decisional capacity to understand the information presented to them
- Be provided complete information about the study in order to make an informed decision

This module has examined:

- Information that should be included during the informed consent process
- The types of situations that can be considered for waiver of informed consent
- The appropriate involvement of ***legally authorized representatives*** for consent
- Obtaining consent from vulnerable populations, e.g. ***pregnant*** women, ***prisoners*** and ***children***
- The need to undertake community consultation when the individual's interests are intimately entwined with their community's interests

Protecting Human Research Participants

NIH Office of Extramural Research

Beneficence

What This Module Covers:

- Risks and benefits
- Privacy and Confidentiality
- Institutional Review Boards (IRBs)
- Data and Safety Monitoring

The Objectives For This Module Are:

- To understand what aspects of research may constitute a benefit to research participants
- To identify possible risks to be considered in evaluating research
- To discuss methods to protect privacy of individuals and confidentiality of data
- To define the role of an IRB to ensure the rights and welfare of human subjects and
- To outline requirements for Data and Safety Monitoring for ***clinical trials***

Beneficence

> Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term beneficence is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation.
>
> – Belmont Report

Two general rules have been articulated as complementary expressions of beneficent actions:

1. Do no harm
2. Maximize possible benefits and minimize possible harms

Investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation.

Risk

Risk is the “probability that a certain harm will occur.” [2]

All research involves some level of risk. We often think of risks in terms of physical harms that may occur as a result of participation in research protocols, but harms may also result from aspects of participation other than from research procedures. For example, harms may result from simply agreeing to be a participant in research, or they may result from disclosure of findings from a research study.

Most risks encountered by participants in research fall into the following categories: [3]

A. Physical

Physical risks may include pain, injury, and impairment of a sense such as touch or sight. These risks may be brief or extended, temporary or permanent, occur during participation in the research or arise after.

B. Psychological

Psychological risks can include anxiety, sadness, regret and emotional distress, among others. Psychological risks exist in many different types of research in addition to behavioral studies.

C. Social

Social risks exist whenever there is the possibility that participating in research or the revelation of data

collected by ***investigators*** in the course of the research, if disclosed to individuals or entities outside of the research, could negatively impact others' perceptions of the participant. Social risks can range from jeopardizing the individual's reputation and social standing, to placing the individual at-risk of political or social reprisals.

D. Legal

Legal risks include the exposure of activities of a research subject **"that could reasonably place the subjects at risk of criminal or civil liability."** [4]

E. Economic

Economic risks may exist if knowledge of one's participation in research, for example, could make it difficult for a research participant to retain a job or to find a job, or if insurance premiums increase or loss of insurance is a result of the disclosure of research data.

Minimal Risk

Recall that the principle of beneficence involves maximizing possible benefits and minimizing possible harms to research participants. All research involves some degree of risk; however, some research is considered to be of ***minimal risk***

.

Minimal risk is defined in the Common Rule to be “that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” (**45 CFR 46.102 (i)**)

Types of Risk

Because research involves risks, ***investigators***, Institutional Review Boards (IRBs), and other members of the research team must take responsibility for protecting participants against the risks of participating in research. Protections vary according to the kind of risk:

A. Physical

In many situations, physical risks in research can be minimized by carefully and skillfully following protocols, by having trained individuals conduct research procedures, through careful monitoring of research participants' health status, by recruiting appropriate populations, and by providing clinical care when needed.

B. Psychological

Possible ways to protect against psychological risks include reminding participants of their right to withdraw from research or limit their participation if they become uncomfortable, providing counseling or psychological support for participants who experience distress, or thoroughly debriefing research participants after research sessions are completed.

C. Social

Often, minimizing social risks to participants involves protecting confidential data, including not only the data collected, but the fact of participation in the research project itself.

D. Legal

Protections against legal risks often involve protecting the confidentiality of research data. For studies conducted in the United States, investigators can apply for **Certificates of Confidentiality**, which are intended to prevent investigators from being forced to disclose data that can be linked to identifiable

research participants in legal proceedings.

E. Economic

Protecting confidentiality of data is one method for protecting against economic risks, such as those to employability and insurability. Investigators may elect to keep research data separate from medical records in order to prevent employers and insurance companies from obtaining information that could put the participants at risk.

Examples of Risk and Appropriate Protections

If you are having trouble viewing the interactive content, please click here to go to a text only version

Designing Research: Anticipated Benefits Greater than Potential Harms

In general, the goal of research is to benefit society by contributing to generalizable knowledge about diseases, disorders, public health concerns, etc. Participation in research may:

- Benefit individual participants or communities
- Neither benefit nor harm individual participants or communities
- Pose risks to individual participants

The HHS regulations apply specifically to individual participants in research and require that:

- Risks are minimized
- Unavoidable risks are justified as necessary for sound scientific design
- Research studies are anticipated to make progress toward important, generalizable knowledge

Regulatory Requirement for Explaining Benefits and Risks

After minimizing risks to the extent possible, the HHS regulation requires that ***investigators*** consider:

1. **Protections against risks**: Where appropriate, investigators must describe procedures for minimizing potential risks, including risks to confidentiality, plans for ensuring any necessary medical or professional intervention, plans for data and safety monitoring for ***clinical trials***, etc.
2. **Potential benefits to individual participants**: The proposed research has a favorable ratio of potential benefit to risk. This balancing act is often called a **risk-benefit analysis**
3. **Importance of the knowledge to be gained**: Investigators reasonably anticipate that the research will contribute to generalizable knowledge. This generalizable knowledge is considered a benefit to others, and risks to research participants must be reasonable in relation to the importance of the knowledge that reasonably may be expected to result

Compensation for Research Participation

Some types of research involve a significant commitment from research participants in terms of time or effort, and ***investigators*** may wish to provide ***compensation***.

Institutions should consider establishing standards for fair and appropriate compensation.

During the ***informed consent*** process, investigators should explain to potential research participants:

1. If there will be compensation for their participation in the research
2. Appropriate expectations for receiving full, partial, or no compensation if research participants complete the study or withdraw prior to its completion
3. That compensation is meant to reimburse research participants for their time, research-related inconveniences and/or research-related discomforts

Compensation **is not** a benefit of the research.

Avoiding Undue Inducement

While the use of **inducements** to participate in research is considered appropriate under many circumstances, sometimes inducements can be unduly influential and inappropriate. These are referred to as **undue inducements**. As discussed in the **Respect for Persons** section, the level and kind of ***compensation*** must take into consideration the vulnerabilities of the research population to minimize the possibility of undue inducement.

"Undue inducements are troublesome because:

1. offers that are too attractive may blind prospective subjects to the risks or impair their ability to exercise proper judgment; and
2. they may prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling — or continuing — as participants in a research project." [5]

Careful consideration of compensation is not only critical for beneficence, but may be critical for sound research. Considerations should include, but are not limited to, issues like participants' "medical, employment, and educational status, and their financial, emotional, and community resources." [5]

Avoiding the Therapeutic Misconception

Some research studies include examinations, diagnostic tests, and/or interactions with healthcare providers in addition to experimental interventions. These aspects of a research protocol may benefit participants by helping them to better understand a disease or condition, and may help in the participants' medical decision-making. While it is often appropriate to include treatment procedures in the conduct of research studies, there is a risk that research participants may misunderstand the benefits of research if they think that potential benefits of participation in research are certain. This is called the ***therapeutic misconception***

. Therapeutic misconception is the tendency for research participants to:

"… downplay or ignore the risks posed to their own well-being by participation … [due to] the participants' deeply held and nearly unshakeable conviction that every aspect of their participation in research has been designed for their own individual benefit." [6]

Investigators should discuss the risks and benefits of research as part of the ***informed consent*** process in order to minimize the possibility of therapeutic misconception.

Assessing Risks and Potential Benefits

Assessing risks and potential benefits is inexact, but ***investigators*** need to be able to explain to the funding agency, the IRB and the potential research participants how and why the potential benefits of research outweigh the risks of participating in a particular study.

The principle of beneficence requires that investigators consider a number of factors including:

- ***Equipoise***
- Protecting the privacy of research participants and the confidentiality of research data
- Establishing oversight mechanisms to protect the rights and welfare of research participants and to determine the significance of the data

Equipoise and Importance of Knowledge to be Gained

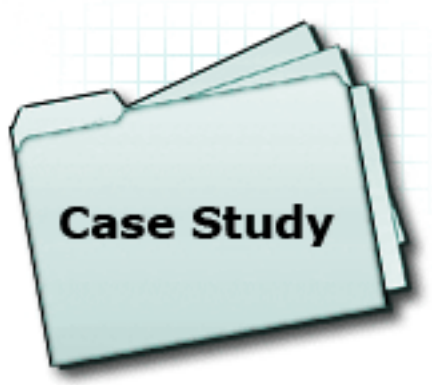
A state of "***equipoise***" is required for conducting research that may pose risks to research participants.

For a ***clinical trial*** to be in equipoise, ***investigators*** must not know that one arm of a clinical trial provides greater efficacy over another, or there must be genuine uncertainty among professionals about whether one treatment is superior than another. [7]

Equipoise is essential for obtaining generalizable knowledge. If a clear and agreed-upon answer exists, asking research participants to assume the risks of research that will provide the same information is not acceptable; no new knowledge will be gained from the study.

Case Study: Equipoise in Research Involving Autistic Children

There are two standard treatments for autistic ***children*** who display a specific set of characteristics. One treatment is a cognitive behavioral intervention, and the other is a dietary and biomedical intervention. Both treatments have equally strong clinical evidence supporting their efficacy. A researcher proposes a comparison of the two interventions to determine which is preferable. The children will be randomized to one of two groups: half of the children will receive the cognitive behavioral intervention and the other half of the children will receive the dietary and biomedical intervention.



Is this study in equipoise?

Yes, this study is in equipoise.

Correct!

This study is in equipoise because there is insufficient data to persuade investigators or physicians that one approach is preferable to the other for a child displaying the specific characteristics.

No, this study is NOT in equipoise.

The correct answer is Yes.

Privacy and Confidentiality

Investigators are responsible for

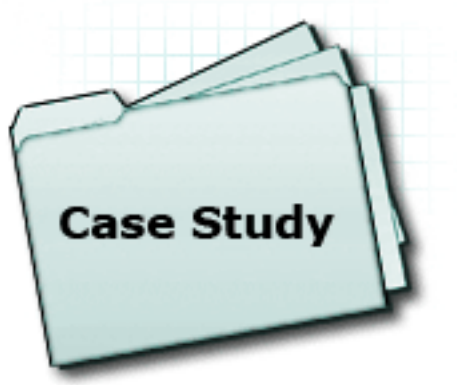
- Protecting privacy of individuals
- Confidentiality of data

Privacy means being "free from unsanctioned intrusion." [8]

Confidentiality means holding secret all information relating to an individual, unless the individual gives consent permitting disclosure. [9]

Case Study: Confidentiality in Clinical Research

After the conclusion of a ***clinical trial*** in a small rural community, an ***investigator*** is anxious to publish findings. Understanding the NIH policies encouraging the reporting of demographic differences in intervention effect, and concerned about protecting the confidentiality of research participants, the investigator publishes only general demographic data such as sex, age, state, and county.



Is this an appropriate and acceptable way to protect the confidentiality of research participants?

Yes, this is an appropriate and acceptable way to protect the confidentiality of research participants.

The correct answer is No.

Publishing demographic information is only acceptable in situations where the population is large enough, or the disease/condition is common enough that research participants cannot be identified using the demographic data provided. This study was carried out in a small community where it might be

easy to identify participants.

For example, these protections were not sufficient after a hantavirus outbreak on an Indian Reservation in the United States. The information published made the identity of one of the individuals who died obvious to the local tribal leaders. In this case the published report not only compromised the identity of the research participant, it also violated the cultural taboo about not speaking of the recently deceased.

No, this is NOT an appropriate and acceptable way to protect the confidentiality of research participants.

Correct!

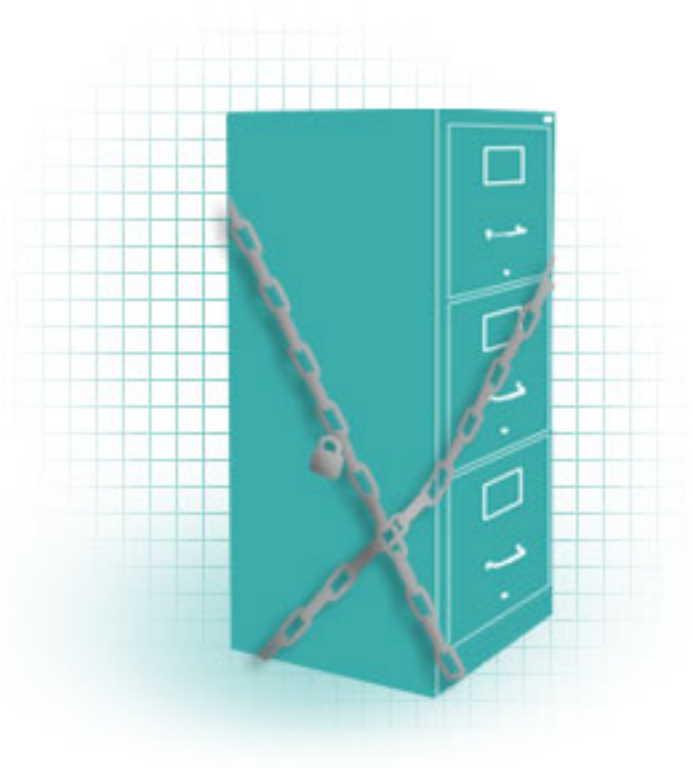
Publishing demographic information is not acceptable in situations where the population is small or the disease/condition is rare because it is possible for research participants to be identified using only general demographic data.

For example, these protections were not sufficient after a hantavirus outbreak on an Indian Reservation in the United States. The information published made the identity of one of the individuals who died obvious to the local tribal leaders. In this case the published report not only compromised the identity of the research participant, it also violated the cultural taboo about not speaking of the recently deceased.

Confidentiality

The need for maintaining confidentiality of private information exists in virtually all studies in which data are collected from or about living individuals. In most research, maintaining confidentiality is a matter of following some established practices, for example:

- Properly disposing of data sheets and other paper records
- Limiting access to identified data; and/or
- Storing research records in locked cabinets or secured databases



It may also be appropriate for ***investigators*** to remove direct identifiers from human specimens and data so that they may be analyzed without risk of accidental disclosure of private information. De-identifying data can be done in several ways, including ***coding*** and ***anonymizing***.

Coded Private Information and Human Subjects Research

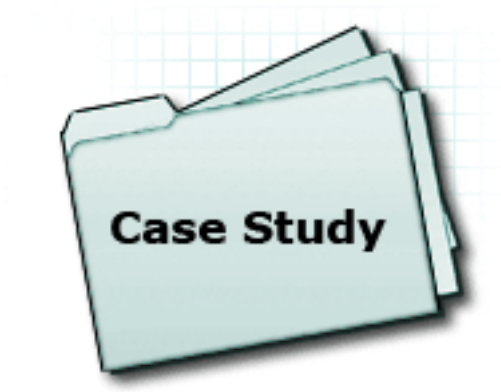
Research with coded private information or specimens involves human subjects if:

1. The private information or specimens were collected specifically for the currently proposed research project through an interaction or intervention with living individuals; or
2. The ***investigator***(s) can readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

Research with coded private information or specimens does not involve human subjects if:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

Case Study: Research with Anonymized Data



You are an investigator proposing to use data from a colleague's database to conduct secondary analyses. You want to examine the behavior and attitudes in male spouses of female business executives. Your colleague will provide coded data for your proposed studies, and you and he enter into an agreement by which he will keep the key to the code and will have no other involvement in the research. Therefore, your colleague is not an ***investigator*** in your research.

Does this study involve human subjects?

Yes, this study involves human subjects.

The correct answer is No.

The study does not involve human subjects because both criteria are met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

The use of anonymized data means that the investigator cannot identify the individuals to whom the data pertain, and obtaining the data from a colleague with whom the investigator is not collaborating means that the colleague will not be able to link any research results to identifiable individuals.

No, this study does not involve human subjects.

Correct!

The study does not involve human subjects because both criteria are met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

The use of anonymized data means that the investigator cannot identify the individuals to whom the data pertain, and obtaining the data from a colleague with whom the investigator is not collaborating means that the colleague will not be able to link any research results to identifiable individuals.

Institutional Review Boards

Institutional Review Boards (IRBs) are specialized committees required by HHS regulations that safeguard the rights and welfare of human subjects. IRBs determine "the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice" (**45 CFR 46.107**).

The major roles of IRBs in the oversight of research are:

1. Initial review and approval or disapproval of the proposed research activity
2. Ensuring that the proposed ***informed consent*** process meets all of the requirements of **45 CFR 46.116**
3. Providing continuing oversight for progress reports and protocols for ongoing research studies

IRB Membership

The HHS regulations (**45 CFR 46.107**) require that IRBs have at least 5 members from a variety of backgrounds. The experience, expertise and diversity of the IRB members should allow the IRB to provide a complete and adequate review of the research activities conducted at the institution.

Research may involve issues about which IRB members lack specific expertise. In these situations, IRBs should identify and invite individuals with specialized knowledge to assist in the review of applications and protocols where the expertise is required.

This issue was raised in the **Respect for Persons** section when discussing the HSS regulations for IRB membership when a study sought to **enroll a vulnerable population (prisoners) in research**. Another example of where specific expertise may be needed is a protocol proposing a study that recruits participants presenting to a hospital Emergency Department (ED) with acute appendicitis. If the IRB lacks expertise about protections for human subjects in emergency situations, the IRB Chair should ask an expert, such as the head of the ED to advise the IRB on the feasibility of the recruitment strategy.

Working with the IRB

Although IRBs and ***investigators*** have different roles in research, they have a ***shared responsibility*** to ensure that research participant protections are appropriate.

As an investigator, you will work most effectively with IRBs if you understand the information that the IRB needs in order to review and approve your proposed research study.

The HHS regulations provide **general criteria** for IRB approval of research, but the specific information that you need to submit may vary among institutions, and may even vary among IRBs at the same institution. You should contact the IRB or Research Administration office at your institution for specific instructions.

General Criteria for IRB Approval of Research (45 CFR 46.111)

- Risks to human subjects are minimized
- Risks to human subjects are reasonable in relation to anticipated benefits, if any, to human subjects and the importance of the knowledge that may reasonably be expected to result from the research
- Selection of human subjects is equitable

- ***Informed consent*** will be sought from each prospective research participant or the prospective research participant's ***legally authorized representative*** in accordance with and to the extent required by the HHS regulations **(45 CFR 46.116)**
- Informed consent will be appropriately documented in accordance with and to the extent required by the HHS regulations (**45 CFR 46.117**)
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of the human subjects, and when appropriate there are adequate provisions to protect the privacy of human subjects and to maintain the confidentiality of data

Expedited IRB Review

Protocols may be reviewed either at a meeting of the full IRB or by "expedited review."

For "certain types of research involving no more than ***minimal risk*** and for minor changes to existing research," an IRB may choose to use an **expedited review procedure**. The expedited review may be conducted by the IRB chair or by designated experienced IRB member(s) (**45 CFR 46.110**).

Investigators should understand that **expedited review** is conducted by fewer individuals, but is no less stringent and not necessarily faster than a **full IRB review**. If any individual reviewer who conducts an expedited review is unable to approve a proposed study, the study must be discussed by the full IRB.

Data and Safety Monitoring

Data and Safety Monitoring Plans describe protections for research participants and data integrity, and oversight for ***clinical trials*** at a level that is commensurate with the risks of participating in the clinical trial. That is, the method and frequency of monitoring is directly related to the possible harms to research participants in the clinical trial.

The HHS regulations require that studies involving human subjects should have a monitoring plan when appropriate (**45 CFR 46.111**).

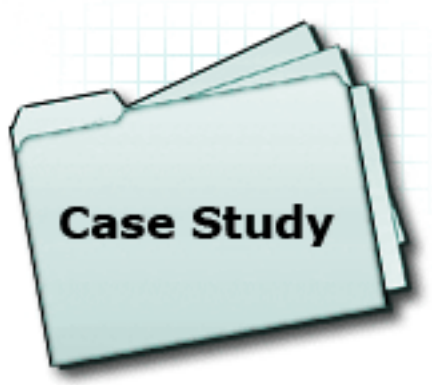
The NIH requires that all clinical trials supported by NIH have a **Data and Safety Monitoring (DSM) plan**.

Data and Safety Monitoring Boards

Appropriate protections and oversight can range from oversight by the Principal ***Investigator*** and IRB for a single-site, ***minimal risk*** clinical trial, to oversight by a full Data and Safety Monitoring Board (DSMB) and IRB(s) for a multi-site trial that involves greater than minimal risk.

DSMBs are committees of experts who have no bias with respect to the research and may be permitted to periodically view unblinded data and conduct interim analyses. Principal Investigators must not view unblinded data while their studies are ongoing because they need to maintain objectivity to the extent possible and to ensure integrity of the accruing data.

Case Study: Reducing Exposure to Mercury



An ***investigator*** proposes to work with the community organization of a population where many of the residents are exposed to high levels of mercury through occupational exposure. A previous study indicated that the harms resulting from exposure to a similar heavy metal contaminant could be mitigated through the use of a behavioral intervention. The investigators propose testing the intervention to see if mercury exposure can be reduced in this population. The research design involves randomizing human subjects either to the experimental behavioral intervention in addition to conventional therapy, or to conventional therapy alone. Should the behavioral intervention be determined to be successful, participants who received only conventional therapy will be offered the behavioral intervention after the completion of the study. Research participants will know which intervention they receive because conventional therapy does not include a behavioral component.

Does this study require a data and safety monitoring plan?

Yes, a data and safety monitoring plan is required.

Correct!

A data and safety monitoring plan is required because the proposed study is a clinical trial.

Investigators are advised to refer to NIH Institute/Center policies and consult with NIH Program Staff in order to determine the appropriate method for data and safety monitoring.

No, a data and safety monitoring plan is not required.

The correct answer is Yes.

A data and safety monitoring plan is required because the proposed study is a clinical trial.

Investigators are advised to refer to NIH Institute/Center policies and consult with NIH Program Staff in order to determine the appropriate method for data and safety monitoring.

Beneficence: Summary

The Belmont principle of beneficence involves maximizing possible benefits and minimizing possible harms to research participants.

Issues covered under Beneficence include:

- Protections against risks
- Definition of ***minimal risk***
- Methods of weighing risks against anticipated benefits
- Potential benefits for the research participants
- The use of ***compensation*** for participation in research
- ***Equipoise*** and need for there to be genuine uncertainty about whether one treatment is superior to another
- Privacy & Confidentiality of research participants and research data
- Use of coded private information to protect confidentiality
- Use of an IRB to provide oversight for research involving human subjects
- Situations that allow for an IRB expedited review procedure
- Data and Safety monitoring for ***clinical trials***

Protecting Human Research Participants

NIH Office of Extramural Research

Justice

What This Module Covers:

- Fair distribution of the benefits and burdens of research
- Inclusion of Women, Minorities, and ***Children*** in Research
- Issues to consider in international research

The Objectives For This Module Are:

- To understand the concept of fair and equitable sharing of the benefits and burdens of research
- To learn about NIH policies on inclusion of women, minorities, and children in research

Protecting Human Research Participants

NIH Office of Extramural Research

Justice

> Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.
>
> – Belmont Report

The definition of justice has two parts:

- Fair procedures and outcomes are used to **select** research participants, and
- There is a fair distribution of benefits and burdens to populations who **participate** in research

Individual Justice and Social Justice

The Belmont Report distinguishes social justice and individual justice in the selection of subjects:

Individual justice requires that ***investigators*** "should not offer potentially beneficial research only to some patients who are in their favor or select only 'undesirable' persons for risky research."

Social justice "requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons."

More on Social Justice

"The choice of participants in research needs to be considered carefully to ensure that groups (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are not selected for inclusion mainly because of easy availability, compromised position, or manipulability." [10]

Selection should depend on reasons directly related to the research questions. When research leads to the development of new treatments, procedures, or devices, justice demands both that:

- These advancements are provided to those who can benefit from them, and
- The research should involve persons from groups who are likely to benefit from subsequent applications of the research

Equity vs. Equality in Human Subjects Research

The meanings of “equity” and “equality” are similar, but not the same. The difference between equity and equality has important implications for justice in research.

To treat **“equitably”** means to treat fairly;
To treat **“equally”** means to treat in exactly the same way.

Research should strive for equitable distribution of the risks and potential benefits of the research. This means that ***investigators*** are treating the groups involved in the research fairly and justly. It does not necessarily mean that all groups are equally represented, but that their representation is fair and just based on the risks and potential benefits associated with the research.

Equitable Distribution

In order to achieve an equitable distribution of the risks and potential benefits of the research, ***investigators*** must determine the distribution of different groups (men and women, racial or ethnic groups, adults and ***children***, age, etc.) in the populations that:

1. May be affected by the disease or condition under study, and
2. That are anticipated to benefit from the knowledge gained through the research

Challenges to Achieving an Equitable Distribution of Benefits and Burdens

Investigators must ensure that the participants recruited for the research will not be ***unduly burdened*** and that recruitment reflects the diversity of the population that may benefit from the knowledge generated from the study.

Individuals with the advantages of wealth and education may have an unfair advantage in terms of reaping the benefits of research because they may be able to afford new and costly treatments more easily than individuals in resource-poor settings.

NIH Inclusion Policies: Women and Minorities

One way the justice principle is applied is through the **Inclusion of Women and Minorities As Participants In Research Involving Human Subjects**. Because knowledge gained from clinical research may define health policy and shape standards of care for all patients, it is important to consider whether the intervention or therapy under scrutiny "affects women or men or members of minority groups and their subpopulations differently."

It is important to include women and members of minority groups and their subpopulations in all NIH–funded clinical research.

Case Study: Migraine Intervention Trial

A researcher seeks to improve treatment for severe migraines that are partially responsive to oral medication. He proposes to test whether acupuncture, in addition to a sufferer's oral medication, is more effective treatment than oral medication alone. Because **women are three times more likely to experience migraines than men**, he proposes to enroll three times as many women as men. They will be recruited from racially and ethnically diverse communities.

Does this study design fulfill the principle of justice?

Yes, this study design does fulfill the principle of justice

Correct!

The research includes women and men in proportion to the rates of severe migraines experienced by each sex, and is designed to have racial and ethnic diversity. The study provides both sexes and racial/ethnic communities with the opportunity for benefits from the ***clinical trials***, and does not unfairly burden any single group with the risks of research. Its design is fair.

No, this study design does not fulfill the principle of justice

The correct answer is Yes.

The study includes women and men in proportion to the rates of severe migraines experienced by each sex, and is designed to have racial and ethnic diversity. The study provides both sexes and racial/ethnic communities with the opportunity for benefits from the ***clinical trials***, and does not unfairly burden any single group with the risks of research. Its design is fair.

Case Study: Esophageal Cancer

A group of ***investigators*** proposes to investigate genetic factors that may increase risks for esophageal cancer. Genetic factors in esophageal cancer are not well understood and esophageal cancer occurs in many racial and ethnic populations. The investigators propose to collect DNA from cheek swabs and administer a risk factor questionnaire. Both cancer patients and age-matched controls will be included.

The investigators have access to a predominantly Caucasian sample, and have no plans to recruit participants outside of their available pool.

Is this an acceptable strategy?

Yes, this is an acceptable strategy

The correct answer is No.

The NIH inclusion policies require that inclusion be generalizable to the population of the United States. Acceptable inclusion of women and/or minorities depends both upon the scientific question addressed by the study and the prevalence of the disease, disorder, or condition in these populations.

In this case, it is scientifically appropriate to include a broad population. Failure to include groups that would be affected by this condition could result in gaps in scientific knowledge.

No, this is not an acceptable strategy

Correct!

The NIH inclusion policies require that inclusion be generalizable to the population of the United States. Acceptable inclusion of women and/or minorities depends both upon the scientific question addressed by the study and the prevalence of the disease, disorder, or condition in these populations.

In this case, it is scientifically appropriate to include a broad population. Failure to include groups that would be affected by this condition could result in gaps in scientific knowledge.

Inclusion of Children in Research

NIH also applies the principle of justice through the **NIH Policy and Guidelines on the Inclusion of Children as Participants in Research**.

The policy emerged from the observation that children have often received treatments that have only been tested in adults, and that there is insufficient data on safe and effective uses for many treatments provided to ***children***. Although the past practice of excluding children may have stemmed from good motives, "protecting" children in this way has resulted in:

1. Denying children the benefits of participation in research, and
2. Preventing the collection of sufficient data about the effects of agents in children

Excluding Children from Research

The **NIH Policy and Guidelines on the Inclusion of Children in Research** states that ***children*** must be included in all NIH-supported human subjects research unless "… there are scientific and ethical reasons not to include them."

If an ***investigator*** proposes to conduct clinical research that does not include children, the exclusion of children must be fully justified using one or more of the exceptions described in the Policy.

Policy Exceptions

1. The research topic to be studied is irrelevant to children …
2. There are laws or regulations barring the inclusion of children in the research …
3. The knowledge is already available for children or will be obtained from another on-going study, and an additional study will be redundant …
4. A separate, age-specific study in children is warranted and preferable …
5. Insufficient data are available in adults to judge potential risk in children … in some instances, the nature and seriousness of the illness may warrant [children's] participation based on careful risk and benefit analysis ...
6. The study design is aimed at collecting additional data on pre-enrolled adult study participants …
7. Other special cases justified by the investigator and found acceptable to the review group and Institute Director

Definiton of Children: HHS Regulations and NIH Policy

Although the HHS Regulations and the NIH Inclusion Policies apply to research involving children, they vary in their definitions of ***children***.

HHS regulations

NIH Inclusion Policy

Research conducted or supported by the NIH must follow **both** the HHS requirements for protections and the NIH requirements for the inclusion of children.

Click here for an exercise in subject selection

Justice and the Use of Placebos

The use of ***placebos*** in clinical research is relevant to all the issues addressed in this course. It raises issues related to justice, respect for persons, and beneficence. All three principles address a researcher's duty not to exploit or ***deceive*** research participants and to treat them fairly.

Risks associated with the use of placebos in research are:

If you are having trouble viewing the interactive content, please click here to go to a text only version

The principle of Justice requires that when placebos are used, prospective research participants must be treated fairly. Unless justifications for a waiver are approved, the ***informed consent*** process must disclose sufficient information to ensure that potential research participants:

- Understand what placebos are
- Understand the likelihood that they will receive a placebo

Are able to provide their fully informed consent that they are willing to receive a placebo

Justifying the Use of Placebos

Examples of justifications for the use of ***placebos*** include:

1. When there are no approved, effective treatments for the condition, or
2. If there is disagreement about whether standard treatment is better than placebo, or
3. When the additional risk posed by the use of placebo is minor and withholding the current standard therapy would not lead to serious or permanent harm, or
4. If the study is anticipated to result in widespread or major benefits and the receipt of placebo by individuals poses ***minimal risk***

Incomplete Disclosure and Deception

Incomplete disclosure and ***deception*** may be useful for some research goals, but researchers may use them only after thorough consideration of:

- Whether the scientific goals of the research can be achieved by methods that do not involve incomplete disclosure or deception
- Whether participants would consider the information withheld during the ***informed consent*** process important to their decision to participate in the study
- Whether it is possible to inform participants that they will only learn about all the goals of the research after the research study is over

Waiver of Informed Consent

Incomplete disclosure and deception present challenges to justice because prospective participants' "***informed consent***" will not be fully informed. HHS regulations (**45 CFR 46.116(d)**) allow informed consent to be waived only if:

- Participation in the research involves no more than ***minimal risk***
- The waiver must not adversely affect the rights and welfare of research participants
- ***Incomplete disclosure*** or ***deception*** must be essential to the ability to carry out the research
- Whenever appropriate, research participants will be given additional pertinent information after they have participated in such a study (debriefing)

To Debrief or Not to Debrief

Debriefing of research participants after the study involves an explanation of the ***deception*** or ***incomplete disclosure*** of research goals to participants as well as a complete disclosure of the true goals of the research. Debriefing is generally considered to be appropriate, but must depend on whether the disclosure will result in harm.

Debriefing is appropriate when it will **benefit the research participant's welfare** by:

- "… correct[ing] misperceptions, or
- reduc[ing] pain, stress, or anxiety concerning the [research participant's] self-perception or performance …"

Fairness in International Research

When HHS-supported research takes place outside of the United States questions about fair treatment and fair standards may arise. This may be especially true of research conducted in countries where:

- Resources may be scarce and/or
- Other vulnerabilities may be pronounced

A few of the many issues that demand careful consideration with respect to justice, as well as beneficence and respect for persons, include:

- How can research conducted in resource-poor setting avoid exploiting participants?
- What is owed to participants in clinical research and to the population of the host country after studies are complete?
- In addition to following the HHS regulations, what standards and assurances to protect research participants should ***investigators*** and non-US institutions use when conducting research abroad?
- How can regional or cultural differences be negotiated?
- For settings where cultural values impact ***informed consent***, how should processes be altered?

Sustaining Benefits Locally

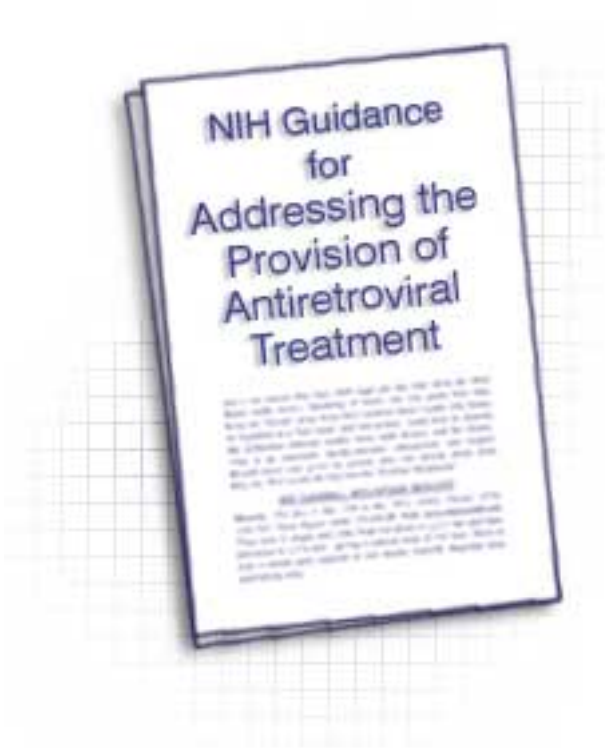
Investigators should think about how benefits to individual research participants and the local population may be sustained after the study is complete.

When planning a study, researchers and sponsors may:

- "… make reasonable, good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have proven effective for the participants …" [11]
- Consider how any effective treatment emerging from the research could be provided to the rest of the population

Sustaining Benefits for Participants with HIV/AIDS in NIH-Supported Clinical Trials of Antiretroviral Agents

The NIH values continued treatment for research participants in HIV/AIDS antiretroviral studies.



*"For antiretroviral treatment trials conducted in developing countries, the NIH expects **investigators**/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial. The NIH recommends investigators/ contractors work with host countries' authorities and other stakeholders to identify available sources of antiretroviral treatment."*

Information is found in the **NIH Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries**.

Standards and Assurances for International Research

The HHS Office for Human Research Protections (OHRP) has set the expectation that the HHS regulations, as well as any additional **institutional and local standards**, will be followed in all research conducted or supported by HHS.

Investigators:

If you plan to engage in NIH-funded research in non-U.S. settings you must comply with the protections and standards set out in the HHS regulations Subpart A. Researchers may go beyond HHS regulations, however, to meet the ethical, legal, and social standards for the local setting.

Institutions:

Non-U.S. institutions engaged in HHS-conducted or -supported human subjects research must obtain an international (non-U.S.) Federalwide Assurance (**FWA**) from OHRP.

IRB Review for Research in International Settings

Institutions have a profound responsibility to ensure that all IRBs designated under Federalwide Assurance possess sufficient knowledge of the local research context to satisfy the requirements for human subjects protections regardless of the IRB's geographic location relative to the institution and the research.

Knowledge of the local context may be provided by:

- Specialists with personal, direct knowledge of the local research context who participate in IRB discussions and provide insight on achieving protections for research participants
- An IRB situated within the local research context

Local Cultural Norms and Informed Consent

In unfamiliar settings, ***investigators*** should:

- Become familiar with local cultural norms and
- Seek guidance from community advisors and the IRB

Investigators should incorporate cultural norms into the research process whenever possible and appropriate. Examples of cultural norms include **community consent** and ***informed consent*** **from family representatives**

:

If **community consent** is the cultural norm, it may be appropriate to obtain community consent in advance of obtaining informed consent from individuals. Community consent cannot replace the informed consent from individuals.

If cultural norms require ***permission*** from a family member before an individual may enroll in research, it may be appropriate to obtain permission from the family member in addition to informed consent from the prospective research participant.

Justice: Summary

Justice requires:

- Fair procedures and outcomes in the selection of research participants, and
- Distribution of benefits and burdens among the populations participating in research.

Individual justice requires that:

- Benefits of participation in research are offered to a diverse eligible population, and
- Risks of participation in research are shared by a diverse population

Social justice requires that consideration is given to classes of subjects that ought, and ought not, to participate in research. Considerations are based on:

- The ability of members of that class to bear burdens and
- The appropriateness of placing further burdens on already burdened persons.

This section also examines:

- Inclusion of women, minorities and ***children***
- ***Placebos***
- ***Incomplete disclosure*** and ***deception***
- Debriefing participants after the study
- International research
- Research in resource-poor countries

This section also discusses the NIH guidelines regarding continued treatment for research participants in HIV/AIDS antiretroviral studies.

Conclusion

This course is designed to provide a minimum level of knowledge that an individual should have before designing a protocol for research involving human subjects.

There are numerous additional sources of training on this topic. Some are provided through:

- The NLM **Bioethics Information Resources** and through
- The **HHS Office of Research Integrity RCR Resources — Human Subjects**

Further Training

You may wish to consult NIH staff and resources about research participant protections, such as:

- Scientific Review Officers
- Program Directors
- Specialized offices within the NIH Institutes/Centers
- The **NIH Office of Extramural Research Human Subjects** Web site
- NIH Grants Info: **grantsinfo@nih.gov**

You may also have access to resources at your institution or at nearby institutions, such as:

- IRBs
- IRB Administrators
- Experienced clinical investigators
- Hospital Ethics Committees
- Former research participants
- Advocacy groups
- Communities of potential participants
- Professional Societies

Staying Current

The material in this course will be updated periodically to reflect current issues.

Institutions and investigators that are using this Web-based training to meet the NIH requirement for **Required Education in the Protection of Human Research Participants** should check back at least once a year to be sure that your knowledge reflects the most current thinking on the various topics.

We welcome your feedback and suggestions on the material covered in this course.

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z

A

Anonymized data —

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Lacking “identifiers or codes that can link a particular sample to an identified specimen or a particular human being.”

*Source: 2000. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance, Executive Summary. Rockville, MD: National Bioethics Advisory Committee: p. 2. (**http://bioethics.georgetown.edu/nbac/hbm_exec.pdf**)*

Close Window

Assent —

Top of Page

“...affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.”

Source: 45 CFR 46.402(b)

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Autonomous person —

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“An individual capable of deliberation about personal goals and of acting under the direction of such deliberation.”

Source: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The

Click here to return to the main menu

*Belmont Report — Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, D.C.: U. S. Department of Health and Human Services: Part B, section 1, "Respect for Persons" (**http://www.nihtraining.com/ohsrsite/guidelines/belmont.html**)*

Close Window

B

C

Children —

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"Persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."

Source: 45 CFR 46.402(a)

Close Window

Clinical trial —

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"...a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices)."

*Source: US Department of Health and Human Services Grant Application (PHS 398) Part II: Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan (**http://grants.nih.gov/grants/funding/phs398_ver0406/HumanSubjects.pdf**)*

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Coded data — Top of Page

Identifiers are removed from the data in exchange for codes that correspond to the identifiers, and the identifiers are maintained separately from the rest of the dataset.

Close Window

Coercion — Top of Page

Influencing an individual's decision about whether or not to do something by using explicit or implied threats (loss of good standing in a job, poor grades, etc.).

Source: Faden, R and T Beauchamp. 1986. A History and Theory of Informed Consent. NY: Oxford University Press, p. 339.

Close Window

Compensation — Top of Page

May include money, other material compensation, such as a coupon or gift certificate, or other non-monetary rewards.

Close Window

D

Deception — Top of Page

Misleading research participants about the research purpose or procedures.

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Click here to return to the main menu

Delivery —

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"Complete separation of the fetus from the woman."

Source: 45 CFR 46.202(b)

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Diminished autonomy —

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An individual with restricted capability of deliberation about personal goals and of limited ability to act under the direction of their deliberations.

*Developed in contrast to the concept of the "autonomous person" in The Belmont Report. Source: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report — Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, D.C.: U.S. Department of Health and Human Services: Part B, section 1, "Respect for Persons." (**http://www.nihtraining.com/ohsrsite/guidelines/belmont.html**)*

Close Window

E

Equipoise —

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Substantial scientific uncertainty about which treatments will benefit subjects most, or a lack of consensus in the field that one intervention is superior to another.

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F

Fetus —

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"The product of conception from implantation until delivery."

Source: 45 CFR 46.202(c)

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G

H

I

Incomplete disclosure —

Top of Page

Withholding some information in order to conduct an unbiased study, with the understanding that the information could be material to a decision by prospective participants about whether or not to participate in the study.

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Informed consent —

Top of Page

A legally-effective, voluntary agreement that is given by a prospective research participant following comprehension and consideration of all relevant information pertinent to the decision to participate in a study.

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Investigator —

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"OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. Note that if the individuals who provide coded information or specimens collaborate on other activities related to the conduct of this research with the investigators who receive such information or specimens, then OHRP would consider such additional activities to constitute involvement in the conduct of the research. Examples of such additional activities include, but are not limited to: (1) the study, interpretation, or analysis of the data resulting from the coded information or specimens; and (2) authorship of presentations or manuscripts related to the research."

*Source: OHRP, HHS. 2004. Guidance on Research Involving Coded Private Information or Biological Specimens. (**http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf**)*

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J

K

L

Legally authorized representative —

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"An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."

Source: 45 CFR 46.102(c)

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M

Minimal risk —

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"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."

Source: 45 CFR 46.102(i)

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N

Neonates —

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"A newborn."

Source: 45 CFR 46.202(d)

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O

P

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Permission — Top of Page

"The agreement of parent(s) or guardian to the participation of their child or ward in research."

Source: 45 CFR 46.402(c)

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Placebo — Top of Page

An inactive intervention designed to resemble, as much as possible, its active counterpart in clinical research.

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Pregnancy — Top of Page

"Encompasses the period from the implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery." Delivery is the "complete separation of the fetus from the woman…"

Source: 45 CFR 46.202(f)

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Prisoner — Top of Page

"Any individual involuntarily confined or detained in a penal institution. The 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."

Source: 45 CFR 46.303

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R

S

T

Therapeutic misconception —

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The tendency for research participants to: “downplay or ignore the risks posed to their own well-being by participation ... [due to] the participants’ deeply held and nearly unshakeable conviction that every aspect of their participation in research has been designed for their own individual benefit.”

Source: Emanuel, EJ et al., eds. 2003. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore, MD: The Johns Hopkins University Press, p.194.

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U

Undue burden —

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Research populations must not be subject to undue burden, wherein they are “systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons

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directly related to the problem being studied."

*Source: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report — Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, D.C.: U. S. Department of Health and Human Services: Part B, section 3, "Justice" (**http://www.nihtraining.com/ohsrsite/guidelines/belmont.html**)*

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Undue influence —

Top of Page

"An offer of an excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance."

Source: Emanuel, EJ et al., eds. 2003. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore, MD: The Johns Hopkins University Press, p.37.

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W

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X

Y

Historical Events-

Timeline of Events

1932-1972 Syphilis Study at Tuskegee

More information may be found in:

- Brandt, AM. 1978. Racism and Research: The Case of the Tuskegee Syphilis Study. Hastings Center Report 8(6): 21-29 , and in
- Jones, JH. 1993. Bad Blood: Tuskegee Syphilis Experiment. Rev. ed. New York: Free Press

1939-1945 Nazi Medical War Crimes

More information may be found in: Annas, GJ, and Grodin, MA The Nazi Doctors and the Nuremburg Code, Human Rights in Human Experimentation (Oxford University Press, NY) 1992.

1944-1974 Cold War Human Radiation Experiments

The U.S. Government conducted more than 400 experiments to determine the effects of exposure to ionizing radiation on human health or to calibrate instruments designed to detect radiation. Most studies involved minimal risks and most of those involving greater than minimal risks included appropriate informed consent.

There were, however, cases where human subjects suffered physical injuries as a result of participating in studies that offered no prospect of direct benefit, or from interventions that were considered controversial at the time that were presented as standard practice.

1946 Nuremberg Doctors' Trial

The individuals who conducted Nazi experiments during WWII were tried separately from other war criminals because of their professional status as physicians and the horrendous and unique nature of their crimes. They were found guilty of "crimes against humanity."

1947 Nuremberg Code

During the trial at Nuremberg, the judges codified fundamental ethical principles for the conduct of research. The Nuremberg Code set forth ten conditions to be met before research could be deemed ethically permissible. The Nuremberg Code became the first international standard for the conduct of research and introduced the modern era of protection for human research subjects.

1947 American Psychological Association

The American Psychological Association began to develop a code of Ethical Standards that included issues in human subjects research.

1948 United Nations adopted Universal Declaration of Human Rights

The United Nations adopted The Universal Declaration of Human Rights, which was inspired by atrocities committed during World War II and states the conviction that human rights needed to be preserved at the international level.

1953 First U.S. Federal Policy for Protection of Human Subjects

The first U.S. Federal policy for the protection of human subjects was put into place for research conducted at the Clinical Center, NIH. This policy provided a mechanism for prospective review of proposed research by individuals having no direct involvement or intellectual investment in the research. This system is the model for the current IRB system.

1963 Jewish Chronic Disease Hospital Study

Studies were undertaken at the Jewish Chronic Disease Hospital in New York to develop information about the human immune system's response to cancer. Live cancer cells were injected into chronically ill and debilitated patients who were told they were receiving a skin test. The investigators were eventually prosecuted and found guilty of fraud, deceit, and unprofessional conduct.

1963-1966 Willowbrook Study

Studies were carried out at the Willowbrook State School for "mentally defective persons," to gain an understanding of the transmission of infectious hepatitis and, subsequently, to test the effects of gamma globulin in preventing or ameliorating the disease.

Residents of Willowbrook, all of whom were children, were deliberately infected with hepatitis, by ingesting the stools of infected persons or receiving injections of more-purified virus preparations. The investigators maintained that hepatitis infection was inevitable for this population; however, critics asserted that the consent process was unethical because coercive

tactics were employed as only children whose parents gave permission to participate in the studies were admitted to Willowbrook.

1964 Declaration of Helsinki

The World Medical Association drafted the first international agreement recommending ethical standards for clinical research.

The most recent version of the Declaration of Helsinki, in addition to translations of the Declaration into languages other than English, can be found on the WMA Web site.

Like the Nuremberg Code, the Declaration makes informed consent a central requirement for ethical research. The Declaration does, however, allow for surrogate consent when the research subject is incompetent, physically or mentally incapable of giving consent, or a minor. The Declaration, which has undergone multiple revisions, also states that research with these groups should be conducted only when the research is necessary to promote the health of the population represented and when this research cannot be performed on legally competent persons.

1966 Henry Beecher's Publication

Henry Beecher published an article in the New England Journal of Medicine describing 22 cases of human subjects research that involved ethical violations. Beecher argued against increasing regulations and in favor of responsible investigators. His perspective has been cited as influencing Federal policy to outline general requirements for informed consent and to delegate specific standards to local review processes. (Faden&Beauchamp p. 211)

1974 Federal Protections for Human Subject

After the Syphilis Study at Tuskegee was exposed, the Senate Committee on Labor and Human Resources held hearings on this study and other alleged health care abuses. The outcomes of these hearings were:

1. The enactment of the National Research Act of 1974 requiring the Department of Health, Education, and Welfare to codify its policy for the protection of human subjects into regulations; and
2. The formation of the National Commission for the Protections of Human Subjects of Biomedical and Behavioral Research, which drafted the Belmont Report.

1979 The Belmont Report

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued Ethical Principles and Guidelines for the Protection of Human Subjects of Research. This is the cornerstone document of ethical principles and HHS regulations for the protection of research subjects based on respect for persons, beneficence, and justice.

1980 Publication of the FDA Regulations

FDA established regulations for clinical research: Code of Federal Regulations, Title 21, Part 50.

The FDA regulates research involving products regulated by the FDA, including research and marketing permits for drugs, biological products, and medical devices for human use, etc., whether or not HHS funds are used. If HHS funds are used in FDA-regulated research, the research must be compliant with both HHS and FDA regulations. More information about the FDA regulations and FDA-specific requirements can be found at http://www.fda.gov/.

1981 Publication of the HHS Regulations

Publication of ?Final Regulations Amending Basic HHS Policy for the Protection of Human Research Subjects,?: 45 CFR 46.101-124 (The Common Rule).

1982 CIOMS Guidelines

The Council for the International Organization of Medical Sciences (CIOMS) published the International Ethics Guidelines for Biomedical Research Involving Human Subjects (CIOMS Guidelines). These guidelines are designed to assist investigators from technologically advanced countries to conduct ethical research involving human subjects in resource-poor countries. These 15 guidelines addressed issues including informed consent, standards for external review, recruitment of subjects, and more. For further information about CIOMS and the Guidelines, refer to http://www.cioms.ch/

1993-1994 Revelation of Human Radiation Experiments

President Clinton established the Advisory Committee on Human Radiation Experiments to investigate human radiation experiments during the period 1944 to 1974; examine cases in which radiation was intentionally released into the environment for research purposes; identify ethical and scientific standards for evaluating these events; and deliver recommendations to the Human Radiation Interagency Working Group. The Committee recommended government apologies and financial compensation in cases where:

- Efforts were made by the government to keep information secret from these individuals, their families or the public to avoid embarrassment or potential legal liability, and where this secrecy had the effect of denying individuals the opportunity to pursue potential grievances
- There was no prospect of direct medical benefit to the subjects, or interventions considered controversial at the time were presented as standard practice, and physical injury attributable to the experiment resulted

See http://www.eh.doe.gov/ohre/roadmap/achre/summary.html for more information

1995 Establishment of The National Bioethics Advisory Commission

The National Bioethics Advisory Commission (NBAC) was established to promote the protection of the rights and welfare of human subjects in research, identify bioethical issues arising from research on human biology and behavior, and make recommendations to governmental entities regarding their application. The NBAC term ended in 2001.

1996 Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule

In response to a congressional mandate in the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the U.S. Department of Health and Human Services (HHS) issued the regulations Standards for Privacy of Individually Identifiable Health Information. For most covered entities, compliance with these regulations, known as the "Privacy Rule", was required as of April 14, 2003.

The Privacy Rule was enacted in response to public concerns over potential abuses of the privacy of health information. Implementation and oversight of the Privacy Rule are the responsibility of the HHS Office for Civil Rights. Additional information about how the Privacy Rule impacts research can be found at http://privacyruleandresearch.nih.gov and at http://www.hhs.gov/ocr/hipaa/

1999 The Death of Jesse Gelsinger

On September 17, 1999, 18 year-old Jesse Gelsinger became the first subject in a gene transfer clinical trial to die from a reaction to a recombinant viral vector. Jesse suffered from a deficiency of ornithine-transcarbamylase (OTC), a necessary enzyme, and enrolled in a Phase I dose-escalation trial at the University of Pennsylvania. The clinical trial involved the injection of an adenoviral vector containing the gene. Jesse died after receiving the injection.

Subsequent investigations found that the Principal Investigator was an inventor for the technology used in the trial and held equity in the start-up company to which the technology was licensed. This case brought significant attention to the issue of

financial conflicts of interest in research. Additional information about financial conflict of interest can be found on the NIH Conflict of Interest (COI) Page. The HHS regulations governing conflicts of interest, "Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding is Sought", can be found at 42 CFR 50, Subpart F.

2000 The Office of Human Research Protections

The Office of Human Research Protections (OHRP) was elevated to the level of the U.S. Department of Health and Human Services, replacing the NIH Office for Protection from Research Risks (OPRR). The OHRP provides leadership for all 17 Federal agencies that carry out research involving humans under the Common Rule regulations. The Office has regulatory authority for the protection of human subjects in research and policies and procedures for Institutional Review Boards.

To learn more about OHRP, visit http://www.hhs.gov/ohrp/

2004 The Secretary's Advisory Committee on Human Research Protections

The Secretary's Advisory Committee on Human Research Protections (SACHRP) was established to provide expert advice and recommendations to the Secretary of Health and Human Services and the Assistant Secretary for Health on issues and topics pertaining to or associated with the protection of human research subjects. See www.hhs.gov/ohrp/sachrp.

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Codes and Regulations- page 6 of 19

Review

The Belmont Report identifies three principles essential to the ethical conduct of research with humans.

Which principle(s) from the list correspond to the statements listed below?

Principles: **Beneficence**, **Respect for Persons**, and **Justice**

1. Investigators should allow individuals to make their own decision.
2. Individuals who are less able to make decisions for themselves require additional protections.
3. Investigators should design research studies so as to maximize benefits and to minimize risks to individuals.
4. The burdens and benefits of research should be fairly distributed among individuals, groups, societies, etc.

Answer Key: 1. Respect for Persons, 2. Respect for Persons, 3. Beneficence, 4. Justice

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Respect for Persons - pg 21 of 25

Case Study: Lack of Assent from a Child

A number of issues should be considered to assist with decision-making. First, investigators need to identify the institutional resources available to help decide the appropriate action, e.g. the IRB, the Ethics Committee, a research participant's advocate, the patient's personal physician. Second, the investigators and others involved in the deliberations should consider issues such as:

Is the child old enough to provide assent?

Are there creative strategies the investigators could implement in order to gain the child's cooperation?

Does the study off the prospect of direct benefit to the children enrolled?

How severe is the child's fear? How insistent is he that he not be stuck?

Is there a way to alleviate the child's fear so that he can participate without using coercion or undue influence?

Could the child wait for a year or two and enroll in the study later (once his fear may have decreased)?

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Beneficence- Page 6 of 27

Examples of Risk and Appropriate Protections

Risk Category	Risk Example	Protection Example
Physical	Fatigue	Supervision by physical trainer for signs or measures of fatigue beyond those defined as acceptable in the research protocol.
Social	Stigma	Investigators do not disclose identifiable data to research participant's co-workers.
Psychological	Anxiety	Fiend or spouse can stay with participant during study procedures.
Legal	Disclosure of illegal drug use	Investigators increase protections for individual research participant's data from legal subpoena by obtaining a Certificate of Confidentiality.
Economic	Loss of job or advancement	Investigators do not disclose information data to research participant's employer.

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Case Study: Selecting Populations to Include in Clinical Research

Match the appropriate population on the right with the proposed clinical research on the left:

1) Research on early diagnosis of senile dementia	a) Children only
2) Clinical trail comparing approved treatments for leukemia	b)Children and Adults
3) Experimental behavioral intervention to reduce bullying in elementary school classrooms.	c) Adults only

Answer Key: 1-c, 2-b, 3-1

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Justice and the Use of Placebos

The use of placebos in clinical research is relevant to all the issues addressed in this course. It raises issues related to justice, respect for persons, and beneficence. All three principles address a researcher's duty not to exploit or deceive research participants and to treat them fairly.

Risks associated with the use of placebos in research are:

Therapeutic misconception- The tendency for research participants to: "downplay or ignore the risks posed to their own well-being by participation…[due to] the participants' deeply held and nearly unshakeable conviction that every aspect of their participation in research has been designed for their own individual benefit."

Deception- Misleading research participants about the research purpose or procedures.

The principle of Justice requires that when placebos are used, prospective research participants must be treated fairly. Unless justifications for a waiver are approved, the informed consent process must disclose sufficient information to ensure that potential research participants:

- Understand what placebos are
- Understand the likelihood that they will receive a placebo
- Are able to provide their fully informed consent that they are willing to receive a placebo

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Frequently Asked Questions

Q: I registered for this course before, but now I cannot log in. Why is that?

As of **March 1, 2008**, the NIH Office of Extramural Research (OER) on-line tutorial Protecting Human Research Participants replaced the NCI Human Participant Protections Education for Research Teams course.

The NCI course is no longer available. The OER on-line tutorial is a totally new course, with new content.

If you try to login with a user name/email address or password used for the NCI course, it will not work. To complete the new OER course, you must register by clicking on the “registration form” link or the Register button located at the following URL: http://phrp.nihtraining.com/users/login.php

Q: I registered after March 1, 2008 but cannot log in. Why?

You can log into the course from the login page. Use your email address and password. If you cannot remember your password, click on the link titled Forgot your password? to retrieve it via email.

Q: How do I get my certificate?

You must complete all sections and all quizzes. A check mark will appear next to a section name when you've read it. There are also **four quizzes** that must be completed. A green check mark (✓) will appear to the right of your quiz score when you have answered correctly the required number of questions.

Also, please ensure all pop-up blockers are turned off, as the certificate will open in a new window for your convenience.

Q: I have taken this quiz several times, and I cannot pass. What do I do?

Some quiz questions have multiple answers possible. A radio button ( ) signifies only one possible answer. A check box ( ) signifies many possible answers, and that **there is more than one correct answer**

For example, the ***Respect for Persons*** quiz, 2 questions have more than one correct answer. Please try reviewing the section and taking the quiz again.

Q: How do I change my quiz answers?

You can only change your quiz answers if you have **not** passed the quiz. Once you have passed the quiz, your answers are locked in and can no longer be changed.

Q: I retook the quiz, but the score stayed the same. Why?

Quizzes are automatically updated upon submission. If your quiz score is the same as it was before you retook it, then it's simply a coincidence.

Technical Support Form

If you experience technical problems which the above FAQs do not cover, please fill out our Technical Support Form or contact the webmaster at support@nihtraining.com

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Protection of Human Research Participants

Citations

1. *(Respect for Persons, pg 3 "Informed Consent")*
   Emanuel, EJ et al., eds. 2003. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore, MD: The Johns Hopkins University Press, p.189.

   Close Window

2. *(Beneficence, pg 3 "Risks")*
   Levine, RJ. 1988. Ethics and Regulation of Clinical Research. 2nd Ed. Yale University Press, p.37.

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3. *(Beneficence, pg 3 "Risks")*
   This list originated from: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report -- Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, D.C.: U.S. Department of Health and Human Services: Part C, section 2, "Assessment of risks and benefits"
   http://www.nihtraining.com/ohsrsite/guidelines/belmont.html

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4. *(Beneficence, pg 3 "Risks")*
   45 CFR 46 406.101 (b)(2)
   http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

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5. *(Beneficence, pg 10 "Avoiding Undue Inducement")*
   Penslar, RL and JP Porter, Office for Human Research Protections (OHRP). 2001. IRB Guidebook, 2nd ed.: Ch. III, Section G
   http://www.hhs.gov/ohrp/irb/irb_chapter3.htm

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6. *(Beneficence, pg 11 "Avoiding the Therapeutic Misconception")*
   Emanuel, EJ et al., eds. 2003. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore, MD: The Johns Hopkins University Press, p.194.

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7. *(Beneficence, pg 13 "Equipoise and Importance of Knowledge to be Gained")*
   Freedman, B. 1987. Equipoise and the ethics of clinical research. New England Journal of Medicine, 317 (3):141-145.

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8. *(Beneficence, pg 15 "Privacy and Confidentiality")*
   "Privacy." 2004. The American Heritage Dictionary of the English Language, 4th ed. Boston: Houghton Mifflin Company.

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9. *(Beneficence, pg 15 "Privacy and Confidentiality")*
Modified from: "Confidentiality." 2004. The American Heritage Stedman's Medical Dictionary. Boston: Houghton Mifflin.

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10. *(Justice, pg 4 "More on Social Justice")*
National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report -- Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, D.C.: U.S. Department of Health and Human Services: Part B, section 3, "Justice."
http://www.nihtraining.com/ohsrsite/guidelines/belmont.html

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11. *(Justice, pg 21 "Sustaining Benefits Locally")*
2001. Ethical and policy issues in international research: clinical trials in developing countries (2 volumes). Bethesda, MD: National Bioethics Advisory Commission.
http://www.bioethics.gov/reports/past_commissions/nbac_international.pdf

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