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PROTECTING HUMAN RESEARCH SUBJECTS

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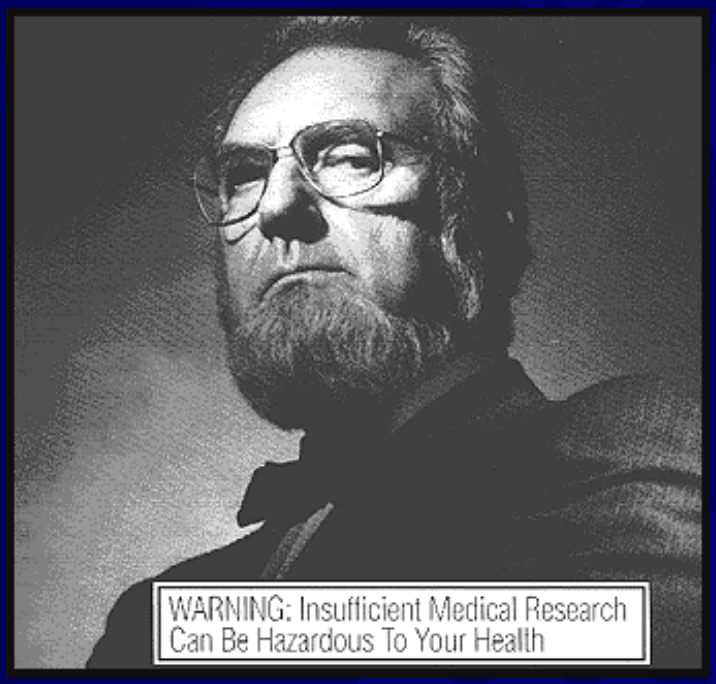

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The mission of the NIH is to improve human health through biomedical and behavioral research. Performing research involving human subjects is a necessary and important part of that mission.

The NIH is committed to assuring that all of its research activities involving human subjects are conducted in a way that promotes their rights and welfare.

Learning Objectives:

Upon completion of this lesson, you should know that:

- **The NIH's Intramural Research Program (IRP) has a Human Research Protection Program (HRPP) which includes policies and procedures for the conduct of research involving human subjects.**
- **There are important historical, legal, and ethical foundations for the NIH's HRPP and its polices and procedures.**
- **The Office of Human Subjects Research (OHSR) is available to help you understand and comply with the requirements of the NIH's HRPP.**

The NIH's Human Research Protection Program (HRPP) is a system of polices and procedures designed to protect the rights and safeguard the welfare of human subjects who participate in research studies in the IRP. In accordance with sound ethical principles and federal legal requirements, NIH has developed policies and procedures to help you understand and fulfill your responsibilities when you conduct or collaborate in research involving humans at the NIH or elsewhere.

The NIH official responsible overall for the IRP's HRPP is the Deputy Director for Intramural Research (DDIR). Dr. Michael Gottesman is the DDIR.

The policies and procedures of NIH's HRPP incorporate:

1. **well established ethical principles for conducting research with humans, and**
2. **requirements of Federal Regulations for the Protection of Human Subjects, Title 45 Part 46 of the Code of Federal Regulations (45 CFR 46).**

In this lesson you will learn more about the ethical principles and legal requirements that underlie the NIH's HRPP and its policies and procedures.

Sometimes it is not easy to see how the policies and procedures of NIH's HRPP apply to particular cases, for example, when your research deals only indirectly with patients or volunteers.

The Office of Human Subjects Research (OHSR) has designed this course to help you identify those research activities which involve human subjects and to help you understand how to protect the rights and welfare of all human subjects involved in your research activities.

This course is not intended to give you "right and wrong" answers to all questions related to your human subjects research. It is designed to provide you with information about the NIH's HRPP and where you can go for help when you need guidance and advice concerning your research activities.

Let's begin by considering a hypothetical collaborative research project involving receipt and analyses of human blood samples in your NIH laboratory.

Hypothetical Collaborative Research Project

Dr. B., an oncologist in an economically underdeveloped country, has been conducting a trial to develop a vaccine against gastric cancer which is highly prevalent in his country.

Hypothetical Collaborative Research Project

Before he began the study, Dr. B. called and asked if you would be willing to perform some research analyses of blood samples to be drawn from subjects in the proposed vaccine trial and to help with the data evaluation. He suggested that you be identified as a co-author on relevant publications.

Hypothetical Collaborative Research Project

You have a long, professional association with Dr. B.

He was a research fellow in your NIH laboratory; you have collaborated on several research projects, and you are co-authors on a number of publications.

Hypothetical Collaborative Research Project

You judged that your role in the research was peripheral (i.e., you would have no contact with human subjects).

You agreed to help and have been receiving and analyzing data and blood samples monthly for a year.

Hypothetical Collaborative Research Project

During a recent interview, Dr. B. said that, without the important input of his colleague at the NIH, the vaccine trial would not have been possible.

A clinical trial with the same vaccine had been planned by researchers in the United States, but was not conducted because of concerns about scientific validity and ethical permissibility.

Hypothetical Collaborative Research Project

A journalist's interest is aroused when he learns that four of ten people in Dr. B's trial had life-threatening adverse events, allegedly from reactions to the vaccine.

Hypothetical Collaborative Research Project

When Dr. B. notifies you that four subjects suffered serious outcomes, you become concerned and question whether or not you have followed the NIH's policies and procedures related to collaborations.

You become more concerned when the journalist calls you and the NIH Freedom of Information Office to request information on the vaccine-related deaths in this research collaboration and your role in the trial.

Hypothetical Collaborative Research Project

The journalist asks you for a copy of the research protocol and the minutes of the NIH Institutional Review Board (IRB) that approved the study.

Hypothetical Collaborative Research Project

You know that IRBs are responsible for reviewing and approving research involving human subjects, but you did not think that NIH IRB approval of this collaboration was necessary because you were only receiving and analyzing blood samples and neither you nor the NIH would have any contact with the human subjects involved in the research.

Hypothetical Collaborative Research Project

You ask your secretary to get the phone number of the journalist and tell him you will call him back. You need help but you are not sure whom to ask.

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The collaborative research activities which you performed in this hypothetical case -- analyses of blood samples drawn specifically for research and analyses of research data -- are considered research with human subjects.

Therefore, before starting the research, you must adhere to relevant NIH policies and procedures which may include seeking review and approval by an NIH IRB for such research collaborations.

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In this case, you did not follow NIH policies and procedures before you performed the sample and data analyses.

- **People were apparently seriously harmed by their participation in research in which you were a collaborator.**
- **You were incorrect in your judgment that the NIH IRB did not need to review and approve the research because you would not have any direct contact with the subjects.**

You will learn more about IRBs as you proceed through this course. The previous case will be discussed further in the Case Study Lesson.

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In order to understand better the reasons for your responsibilities when conducting research involving human subjects, let's review a brief history of the ethical guidelines and the Federal regulations.

The first formal codification of international ethical guidelines for the conduct of research involving humans began in the late 1940's.

In 1946, 23 Nazi physicians went on trial at Nuremberg because of research atrocities performed on prisoners of war.

Nuremburg Trial

Subsequently, in 1947, the Nazi War Crimes Tribunal issued the Nuremberg Code, which was the first internationally recognized code of research ethics.

While the Nuremberg Code and subsequent ethical guidelines represented the most enlightened thinking of the time, many well-intentioned researchers in the United States either did not know about them or did not apply this guidance to their research activities.

Nuremburg Trial

A series of abuses of research subjects came to public attention in the U.S. between 1953 and 1972, including the infamous Tuskegee Study, on the natural history of syphilis, conducted by Public Health Service employees.

These cases led some people to conclude that U.S. researchers could not be trusted to conduct studies involving humans.

More information about historical research cases can be found in the History Lesson.

In the 1950's and 1960's, as federal funding for biomedical research increased dramatically, ethical safeguards and legal requirements were imposed on research activities involving human subjects. The U.S. Government, in dialogue with the research community, gradually designed one of the most comprehensive systems in the world for protecting human subjects.

The protection of human subjects became a central requirement when conducting clinical research.

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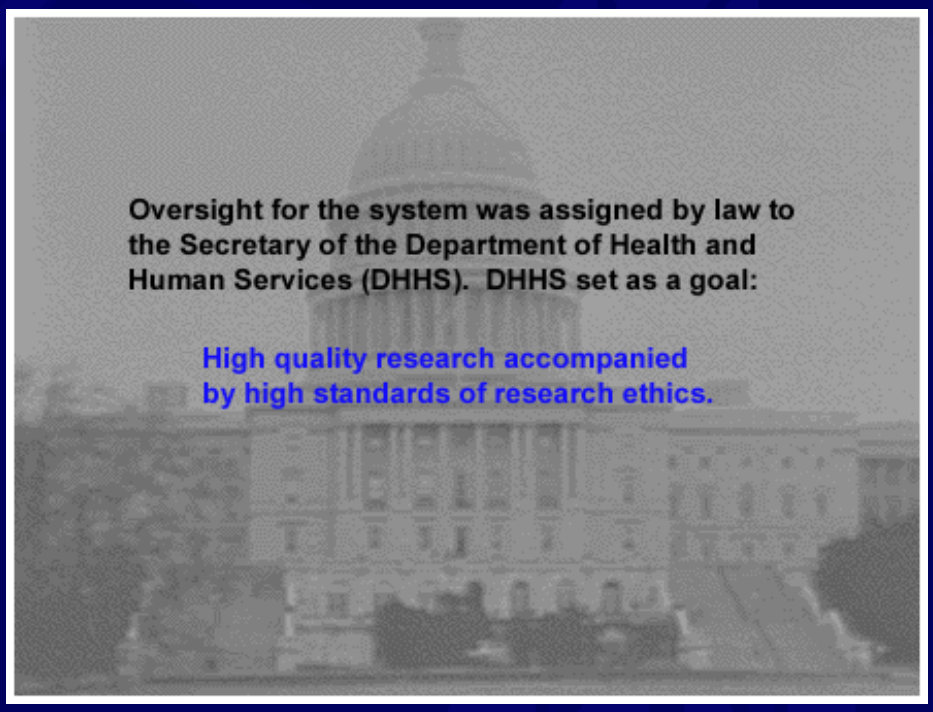
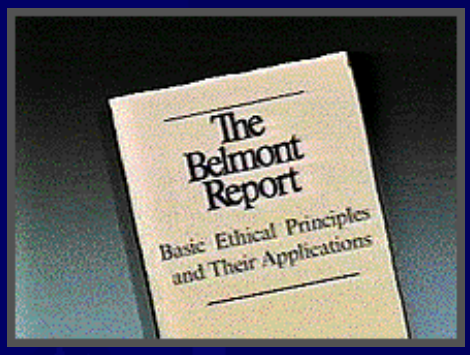
Laws, regulations, and public opinion challenged the research community to make the system operable and accountable.

By Congressional mandate, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974 to make recommendations for the conduct of research involving humans.



The primary task of the National Commission was to identify the ethical principles that would guide all research involving humans. The Belmont Report -- Ethical Principles and Guidelines for the Protection of Human Subjects was published in 1978.

The principles of The Belmont Report govern all research supported by the U.S. government, including that conducted by researchers in the NIH Intramural Research Program (IRP).



These principles are:

1. Respect for Persons: This principle acknowledges the dignity and freedom of every person. It requires obtaining informed consent from research subjects (or their legally authorized representatives).

2. Beneficence: This principle requires that researchers maximize benefits and minimize harms associated with research. Research-related risks must be reasonable in light of expected benefits.

3. Justice: This principle requires equitable selection and recruitment and fair treatment of research subjects.

In the early 1980s, regulations for the conduct of research with humans were published, entitled Title 45 Code of Federal Regulations Part 46, Protection of Human Subjects (45 CFR 46). They have been revised several times.

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In the early 1980s, regulations for the conduct of research with humans were published, entitled Title 45 Code of Federal Regulations Part 46, Protection of Human Subjects (45 CFR 46). They have been revised several times.

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The ethical principles of The Belmont Report are embodied in these regulations. Taken together The Belmont Report and 45 CFR 46 articulate the minimal ethical and legal obligations of those who conduct or support research involving human subjects.

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In the early 1980s, regulations for the conduct of research with humans were published, entitled Title 45 Code of Federal Regulations Part 46, Protection of Human Subjects (45 CFR 46). They have been revised several times.

The ethical principles of The Belmont Report are embodied in these regulations. Taken together, The Belmont Report and 45 CFR 46 articulate the minimal ethical and legal obligations of those who conduct or support research involving human subjects.

Among other things, these regulations require that each institution conducting federally-funded research adheres to the principles of The Belmont Report and sets forth in writing ethical principles, policies and procedures for protecting the rights and welfare of human research subjects. In the Intramural Research Program, this written statement is the NIH Federal-Wide Assurance (FWA).

The FWA is a contract between the NIH and DHHS's Office for Human Research Protections (OHRP) which commits the IRP's HRPP to designing and implementing policies and procedures that protect the human subjects involved in its research activities.

The policies and procedures of NIH's HRPP are found in:

- The standard operating procedures (SOPs) for each of NIH's Institutional Review Boards (IRBs),
- The CC Medical Administrative Series (MAS) (see http://intranet.cc.nih.gov/mec/mas/index.shtml) and
- The Manual Chapter #3014 entitled "NIH Human Research Program" (see http://www1.od.nih.gov/oma/manualchapters/intramural/3014)

You are expected to comply with the requirements of NIH's HRPP.

If you have questions about what is required of you you may contact the NIH Office of Human Subjects Research (OHSR), telephone (301) 402-3444 or discuss them with your Laboratory/Branch/Section Chief.

There is much information about the NIH's HRPP on the OHSR web site at http://ohsr.od.nih.gov.

The NIH's HRPP places shared responsibility for protecting the rights and safeguarding the welfare of human subjects directly on you, as a research investigator, and the NIH, as an institution.

The NIH's HRPP places shared responsibility for protecting the rights of human subjects directly on you, as a research investigator, and the NIH, as an institution.

If in a given situation you are not sure if you are conducting research involving human subjects, you should ask OHSR for resolution. Not knowing or not understanding what the NIH requires of you is not an acceptable reason for ignoring or circumventing its policies and procedures.

The The NIH's HRPP places shared responsibility for protecting the rights of human subjects directly on you, as a research investigator, and the NIH, as an institution.

If in a given situation you are unsure if you are conducting research involving human subjects, you should ask OHSR for a resolution. Not knowing or not understanding what the NIH requires of you is not an acceptable reason for ignoring or circumventing its policies and procedures.

Failure to comply with the NIH's HRPP policies and procedures may constitute unethical behavior and violation of the law, and can lead to loss of research privileges for an individual, a laboratory, or for an entire research program.

The requirements of NIH's HRPP:

- **Apply to all research activities involving human subjects conducted by IRP personnel or supported by IRP contracts or other agreements, and**
- **Requires that all IRP research activities involving human subjects follow the ethical principles of The Belmont Report and the legal requirements of 45 CFR 46.**

Collaboration with researchers in human subjects research activities at other institutions is subject to the requirements of the NIH's HRPP.

For example, collaborative research activities in which subjects are enrolled entirely at a non-NIH site, such as a facility in another country, must meet high ethical standards similar to those required at the NIH.

Federal regulations and the requirements of the HRPP apply to research involving human subjects.

Research means a systematic investigation designed to produce generalizable knowledge.

Research may involve direct interactions or interventions with subjects, such as obtaining data by taking medical histories, obtaining blood samples, urine sampling, diagnostic procedures, or treating patients at least in part for the purpose of gaining generalizable information.

Research may also involve indirect activities such as the analysis of specimens or data from people. Participation in these kinds of indirect activities, particularly if you plan to publish the results (or be a co-author), constitutes human subjects research.

Federal Regulations and the requirements of NIH's HRPP apply to research involving human subjects.

A human subject is a living individual about whom an investigator obtains either (1) data through intervention or interaction with the individual; or (2) identifiable private information.

Research investigators have a fundamental responsibility to safeguard the rights and welfare of the people participating in their research activities. In addition, our society has decided by law that an objective review of human subjects research by a group of diverse individuals is most likely to protect human subjects and promote ethically sound research.

Research investigators have a fundamental responsibility to safeguard the rights and welfare of the people participating in their research activities. In addition, our society has decided by law that an objective review of human subjects research by a group of diverse individuals is most likely to protect human subjects and promote ethically sound research.

Therefore, when conducting research involving humans, Federal regulations and the NIH HRPP both require prospective and continuing review and approval of the research by a committee called an Institutional Review Board (IRB).

IRBs are very important to the conduct of human subjects research at the NIH and other research institutions both inside and outside the U.S.

One reason IRBs are important is because research investigators have an inherent potential conflict of interest. As health care professionals, they are dedicated to promoting the welfare of individual patients.

As researchers, they seek generalizable knowledge applicable to persons other than their individual patients. The second goal may be in conflict with the first.

On the other hand, IRBs have one paramount responsibility:

To protect the rights and welfare of human research subjects.

IRBs at the NIH infrequently disapprove proposed research activities. Instead, they strive to work interactively with research investigators to assure that research design is excellent, that risks are minimized and expected benefits are maximized, and that consent procedures are adequate.

IRB members bring diverse skills, insights, and perspectives to the responsibility of reviewing research activities involving humans.

Although the IRB system is not perfect, conscientious IRBs reassure the American public that the rights and welfare of human subjects are seriously considered by people who do not have a vested interest in the outcome of the research.

By exercising their responsibilities, IRBs promote the protection of human subjects. IRB approval provides a significant affirmation of the scientific and ethical quality of the research, and therefore offers important validation to the research investigator and the research institution.

Keep in mind that the application of ethical principles, the Federal regulations (45 CFR 46), and the requirements of the NIH HRPP are intended to balance society's interest in advancing scientific knowledge with its mandate to protect the rights and welfare of human subjects. IRBs' reviews help to achieve this balance.

Experience has shown that sound ethics and good science are compatible. The system, though not perfect, has worked well in the U.S. for more than 30 years.

The OHSR staff and NIH IRB Chairpersons are available to assist you. If you need advice or guidance, contact OHSR:

NIH, Building 10, Room 2C-146, Bethesda, MD 20892-1154
Phone (301) 402-3444 or FAX (301) 402-3443.

The OHSR website is http://ohsr.od.nih.gov.

Each of the major topics in this Introduction will be described in greater depth in subsequent lessons.

Summary of Important Points in This Lesson

- **The NIH Intramural Program has a Human Research Protection Program (HRPP) which includes policies and procedures for the conduct of research involving human subjects.**
- **The ethical principles of The Belmont Report and the legal requirements of the Federal regulations for the protection of human subjects (45 CFR 46) are incorporated into the requirements of NIH's HRPP.**
- **As an intramural researcher, you are expected to know when the requirements of the NIH HRPP apply to your research.**
- **The OHSR and your NIH IRB Chairpersons are available to assist you in understanding and complying with the policies and procedures of NIH's HRPP.**

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You have completed the Introduction Section of Protecting Human Research Subjects. Please click the main menu at the left to choose the Multiple Project Assurance Lesson.

Learning Objective

This lesson covers several well known instances of unethical research involving human subjects, and provides a historical context for why ethical and regulatory requirements for the conduct of research have been developed over the last 50 years in the United States.

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

- **Recognize some of the ethical violations in research that influenced the development of ethical principles and legal requirements currently governing human subjects research.**

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History Lesson

Until the middle of this century, concerns about the ethics of the practice of medicine centered around therapeutic medicine, not research medicine.

National and international efforts to protect the rights and welfare of human subjects of research have occurred often in response to ethical violations -- situations in which researchers were found to have ignored the fundamental rights of human subjects.

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Infamous Cases: Nazi War Crimes

In order to ensure the supremacy of the Aryan race, the Nazi Party in Germany desired to find a secret way of sterilizing large populations.

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Infamous Cases: Nazi War Crimes

Three experiments involving sterilization were in progress when World War II ended in 1945.

1. Dried plant juice was put into flour that was fed to the general population. This was supposed to sterilize women predominantly.

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Infamous Cases: Nazi War Crimes

Three experiments involving sterilization were in progress when World War II ended in 1945.

2. Intra-uterine injections of a silver nitrate solution were given to women, without their consent, during routine physical examinations.

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Infamous Cases: Nazi War Crimes

Three experiments involving sterilization were in progress when World War II ended in 1945.

3. Men stood at a counter to complete forms while being exposed, without their knowledge, to sterilizing doses of X-radiation.

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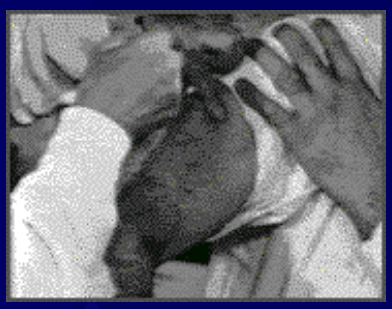
Infamous Cases: Nazi War Crimes

In addition to sterilization experiments, Nazi physician/ researchers were under great pressure to develop an effective vaccine for typhus fever to administer to German troops.

At Buchenwald concentration camp, experiments were conducted in which prisoners were administered vaccine (or placebo) and then injected with blood from patients with typhus fever.



Infamous Cases: Nazi War Crimes

Between 1942 and 1943, about 729 people were subjected to such experiments and 154 died. In addition, other prisoners served as a "passage group." In order to keep the virus alive and virulent, the researchers would inject the virus into prisoners. When these people developed the acute illness, their blood was removed and injected into other prisoners.

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Infamous Cases: Nazi War Crimes

The horrors of the preceding and many other "experiments," were exposed during and after World War II. The people who conducted these experiments were tried separately from other Nazi war criminals because of their professional status as physicians and the atrocious nature of their crimes.

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Infamous Cases: Nazi War Crimes

During the trial at Nuremberg, fundamental ethical principles for the conduct of research involving humans were codified into the Nuremberg Code which sets forth ten conditions that must be met before research involving humans is ethically permissible (e. g., the need for voluntary informed consent of subjects, a scientifically valid research design that could produce fruitful results for the good of society).

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Infamous Cases: Nazi War Crimes

The Nuremberg Code became the first international standard for the conduct of research. If you would like a copy of the Nuremberg Code, you may call OHSR at (301) 402-3444 or obtain it through OHSR's web site at http://ohsr.od.nih.gov

Infamous Cases: Nazi War Crimes

To date, little use has been made of the data generated from the Nazi experiments. There is ongoing discussion in scientific and ethics communities concerning whether it is ethically permissible to use or publish the data.

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Infamous Cases: The Tuskegee Syphilis Study

This study was conducted in the United States and was designed to determine the natural history of untreated latent syphilis.

Over 400 black men with syphilis and about 200 men without syphilis, who served as the controls, were the subjects.

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Infamous Cases: The Tuskegee Syphilis Study

The men were recruited without informed consent. In fact, they were misinformed and told that some of the procedures done in the interests of research (e.g., spinal taps) were actually "special free treatment."

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Infamous Cases: The Tuskegee Syphilis Study

By 1936, it was apparent that many more infected men than controls had developed complications.

Ten years later a report of the study indicated that the death rate among those with syphilis was about twice as high as it was among the controls.

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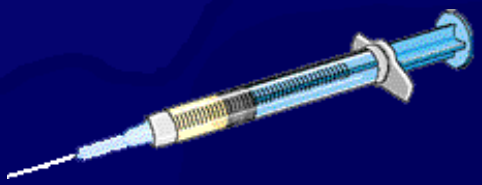
Infamous Cases: The Tuskegee Syphilis Study

In the 1940's, when penicillin, known to be effective in the treatment of syphilis, became available, the men were neither informed of this, nor treated with the antibiotic.



The study continued until the first accounts of it appeared in the national press in 1972, at which time an ad hoc advisory panel was formed by the government to give advice on how to assure that such experiments would never again be conducted.

The government has paid millions of dollars to surviving subjects and the families of deceased subjects.

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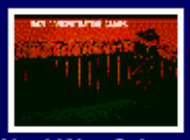

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Infamous Cases: The Jewish Chronic Disease Hospital Study

In 1963, studies were undertaken at New York City's Jewish Chronic Disease Hospital to develop information on the nature of the human transplant rejection process.

These studies involved the injection of live cancer cells into patients who were hospitalized with various chronic debilitating diseases.

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Infamous Cases: The Jewish Chronic Disease Hospital Study

Previous studies had indicated that healthy persons reject cancer cell implants promptly. Patients with widespread cancer also reject homografts, however, rejection is delayed substantially when compared with healthy subjects.

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Infamous Cases: The Jewish Chronic Disease Hospital Study

Researchers said that consent had been given orally, but was not documented. They felt that documentation was unnecessary because it was customary to undertake much more dangerous medical procedures without the use of consent forms.

Further, patients were not told that they would receive cancer cells because, in the view of the investigators, this would frighten the patients unnecessarily. Investigators defended this view on the basis that they had good cause to predict that the cancer cells were going to be rejected.

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Infamous Cases: The Willowbrook Study

From 1963 through 1966, studies were carried out at the Willowbrook State School, a New York State institution for "mentally defective persons."

These studies were designed to gain an understanding of the natural history of infectious hepatitis and subsequently to test the effects of gamma globulin in preventing or ameliorating the disease.

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Infamous Cases: The Willowbrook Study

The subjects, all children, were deliberately infected with the hepatitis virus; early subjects were fed extracts of stools from infected individuals and later subjects received injections of more purified virus preparations.

Investigators defended the deliberate injection of these children by pointing out that the vast majority of them acquired the infection anyway while at Willowbrook, and perhaps it would be better for them to be infected under carefully controlled research conditions.

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Infamous Cases: The Willowbrook Study

During the course of these studies, Willowbrook closed its doors to new residents, claiming overcrowded conditions.

However, the hepatitis program, because it occupied its own space at the institution, was able to continue to admit new patients. Thus, in some cases, parents found that they were unable to admit their child to Willowbrook unless they agreed to his or her participation in the studies.

This case caused a public outcry because of the perception that parents and their children were given little choice about whether or not to participate in research.

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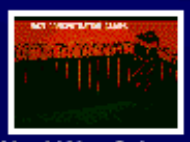
Infamous Cases: Ethical Violations in Research Involving Humans



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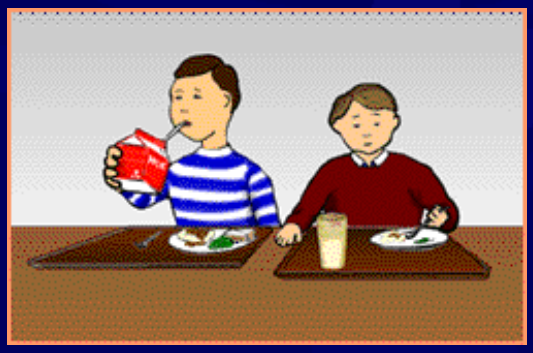
Infamous Cases: Radiation Tests on Mentally Impaired Boys

From 1946 to 1956, 19 boys who thought they were participating in a science club were fed radioactive milk by researchers who wanted to learn about the digestive system.

Infamous Cases: Radiation Tests on Mentally Impaired Boys



The experiments were performed at the Fernald State School in Massachusetts. Researchers from Harvard University and the Massachusetts Institute of Technology fed radioactive forms of iron and calcium to the boys, sometimes in their breakfast milk, to study the body's ability to digest minerals.

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Please choose whatever case you want to see from the history sub-menu or click the Main Menu button to see more of the course.

Learning Objective

This lesson covers several well known instances of unethical research involving human subjects, and provides a historical context for why ethical and regulatory requirements for the conduct of research have been developed over the last 50 years in the United States.

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

- **Recognize some of the ethical violations in research that influenced the development of ethical principles and legal requirements currently governing human subjects research.**

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History Lesson

Until the middle of this century, concerns about the ethics of the practice of medicine centered around therapeutic medicine, not research medicine.

National and international efforts to protect the rights and welfare of human subjects of research have occurred often in response to ethical violations -- situations in which researchers were found to have ignored the fundamental rights of human subjects.

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PROTECTING HUMAN RESEARCH SUBJECTS

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Infamous Cases: Nazi War Crimes

In order to ensure the supremacy of the Aryan race, the Nazi Party in Germany desired to find a secret way of sterilizing large populations.

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Infamous Cases: Nazi War Crimes

Three experiments involving sterilization were in progress when World War II ended in 1945.

1. Dried plant juice was put into flour that was fed to the general population. This was supposed to sterilize women predominantly.

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Infamous Cases: Nazi War Crimes

Three experiments involving sterilization were in progress when World War II ended in 1945.

2. Intra-uterine injections of a silver nitrate solution were given to women, without their consent, during routine physical examinations.

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Infamous Cases: Nazi War Crimes

Three experiments involving sterilization were in progress when World War II ended in 1945.

3. Men stood at a counter to complete forms while being exposed, without their knowledge, to sterilizing doses of X-radiation.

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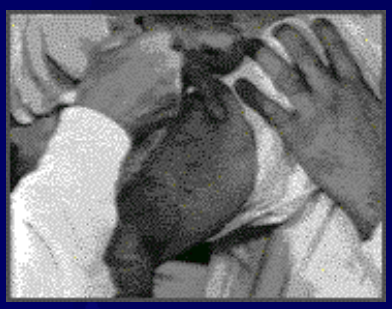
Infamous Cases: Nazi War Crimes

In addition to sterilization experiments, Nazi physician/ researchers were under great pressure to develop an effective vaccine for typhus fever to administer to German troops.

At Buchenwald concentration camp, experiments were conducted in which prisoners were administered vaccine (or placebo) and then injected with blood from patients with typhus fever.



Infamous Cases: Nazi War Crimes

Between 1942 and 1943, about 729 people were subjected to such experiments and 154 died. In addition, other prisoners served as a "passage group." In order to keep the virus alive and virulent, the researchers would inject the virus into prisoners. When these people developed the acute illness, their blood was removed and injected into other prisoners.

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Infamous Cases: Nazi War Crimes

The horrors of the preceding and many other "experiments," were exposed during and after World War II. The people who conducted these experiments were tried separately from other Nazi war criminals because of their professional status as physicians and the atrocious nature of their crimes.

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Infamous Cases: Nazi War Crimes

During the trial at Nuremberg, fundamental ethical principles for the conduct of research involving humans were codified into the Nuremberg Code which sets forth ten conditions that must be met before research involving humans is ethically permissible (e. g., the need for voluntary informed consent of subjects, a scientifically valid research design that could produce fruitful results for the good of society).

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Infamous Cases: Nazi War Crimes

The Nuremberg Code became the first international standard for the conduct of research. If you would like a copy of the Nuremberg Code, you may call OHSR at (301) 402-3444 or obtain it through OHSR's web site at http://ohsr.od.nih.gov

Infamous Cases: Nazi War Crimes

To date, little use has been made of the data generated from the Nazi experiments. There is ongoing discussion in scientific and ethics communities concerning whether it is ethically permissible to use or publish the data.

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Infamous Cases: The Tuskegee Syphilis Study

This study was conducted in the United States and was designed to determine the natural history of untreated latent syphilis.

Over 400 black men with syphilis and about 200 men without syphilis, who served as the controls, were the subjects.

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Infamous Cases: The Tuskegee Syphilis Study

The men were recruited without informed consent. In fact, they were misinformed and told that some of the procedures done in the interests of research (e.g., spinal taps) were actually "special free treatment."

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Infamous Cases: The Tuskegee Syphilis Study

By 1936, it was apparent that many more infected men than controls had developed complications.

Ten years later a report of the study indicated that the death rate among those with syphilis was about twice as high as it was among the controls.

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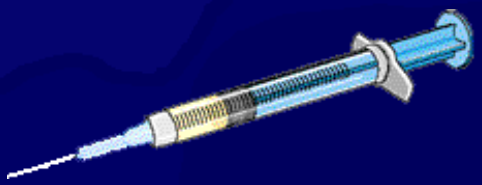
Infamous Cases: The Tuskegee Syphilis Study

In the 1940's, when penicillin, known to be effective in the treatment of syphilis, became available, the men were neither informed of this, nor treated with the antibiotic.



The study continued until the first accounts of it appeared in the national press in 1972, at which time an ad hoc advisory panel was formed by the government to give advice on how to assure that such experiments would never again be conducted.

The government has paid millions of dollars to surviving subjects and the families of deceased subjects.

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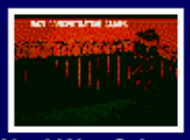

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Infamous Cases: The Jewish Chronic Disease Hospital Study

In 1963, studies were undertaken at New York City's Jewish Chronic Disease Hospital to develop information on the nature of the human transplant rejection process.

These studies involved the injection of live cancer cells into patients who were hospitalized with various chronic debilitating diseases.

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Infamous Cases: The Jewish Chronic Disease Hospital Study

Previous studies had indicated that healthy persons reject cancer cell implants promptly. Patients with widespread cancer also reject homografts, however, rejection is delayed substantially when compared with healthy subjects.

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Infamous Cases: The Jewish Chronic Disease Hospital Study

Researchers said that consent had been given orally, but was not documented. They felt that documentation was unnecessary because it was customary to undertake much more dangerous medical procedures without the use of consent forms.

Further, patients were not told that they would receive cancer cells because, in the view of the investigators, this would frighten the patients unnecessarily. Investigators defended this view on the basis that they had good cause to predict that the cancer cells were going to be rejected.

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Click on The Willowbrook Studies.

Infamous Cases: The Willowbrook Study

From 1963 through 1966, studies were carried out at the Willowbrook State School, a New York State institution for "mentally defective persons."

These studies were designed to gain an understanding of the natural history of infectious hepatitis and subsequently to test the effects of gamma globulin in preventing or ameliorating the disease.

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Infamous Cases: The Willowbrook Study

The subjects, all children, were deliberately infected with the hepatitis virus; early subjects were fed extracts of stools from infected individuals and later subjects received injections of more purified virus preparations.

Investigators defended the deliberate injection of these children by pointing out that the vast majority of them acquired the infection anyway while at Willowbrook, and perhaps it would be better for them to be infected under carefully controlled research conditions.

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Infamous Cases: The Willowbrook Study

During the course of these studies, Willowbrook closed its doors to new residents, claiming overcrowded conditions.

However, the hepatitis program, because it occupied its own space at the institution, was able to continue to admit new patients. Thus, in some cases, parents found that they were unable to admit their child to Willowbrook unless they agreed to his or her participation in the studies.

This case caused a public outcry because of the perception that parents and their children were given little choice about whether or not to participate in research.

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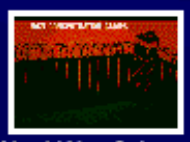

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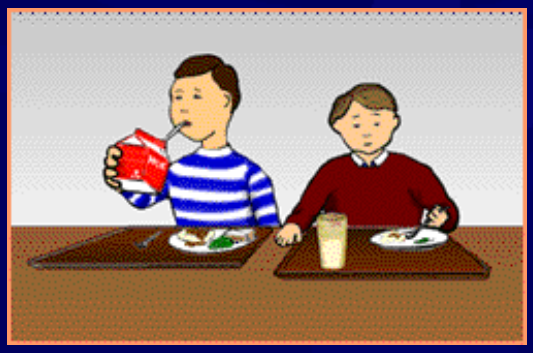
Click on Radiation Tests on Mentally Impaired Boys.

Infamous Cases: Radiation Tests on Mentally Impaired Boys

From 1946 to 1956, 19 boys who thought they were participating in a science club were fed radioactive milk by researchers who wanted to learn about the digestive system.

Infamous Cases: Radiation Tests on Mentally Impaired Boys



The experiments were performed at the Fernald State School in Massachusetts. Researchers from Harvard University and the Massachusetts Institute of Technology fed radioactive forms of iron and calcium to the boys, sometimes in their breakfast milk, to study the body's ability to digest minerals.

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PROTECTING HUMAN RESEARCH SUBJECTS

HUMAN RESEARCH PROTECTION PROGRAM (HRPP)

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NIH's Human Research Protection Program Lesson

The NIH's Human Research Protection Program (HRPP) commits all NIH IRP employees to comply with policies for the protection of human subjects before you begin your research and to continue until you have completed it.

The NIH HRPP sets standards that will enable you to meet both ethical and legal requirements. Failure to comply can delay research, harm subjects, and generate sanctions against an intramural research investigator, a laboratory, or an entire research program.

Learning Objectives

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Upon completion of this lesson, you should be able to identify:

- **Whether NIH policies for the protection of human subjects apply to your research.**
- **When IRB review and approval are required, and when they are not required.**
- **What you are expected to do if your research involves human subjects, but you believe it is exempt from IRB review and approval.**
- **Steps you must take before you collaborate in research involving human subjects with investigators at other institutions.**

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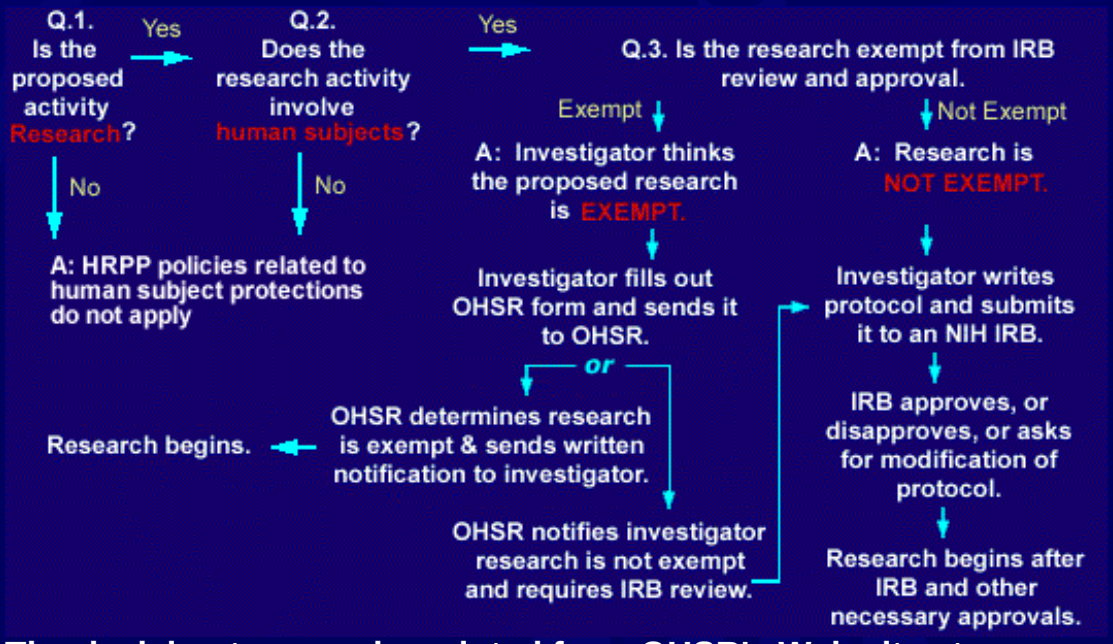
Before beginning a research activity, you need to answer three critical questions about it:

- **Is the activity in which you will be engaged RESEARCH?**
- **Will the activity involve HUMAN SUBJECTS?**
- **Does the activity require IRB REVIEW AND APPROVAL or is it exempt from this requirement?**

The decision tree on the next screen will help you answer these questions.

Here is the decision tree for how to proceed with the review and approval of research involving human subjects.



The decision tree can be printed from OHSR's Web site at http://206.102.88.10/ohsrsite/irb/tree.html.

Let's examine each of the critical questions in more detail, building the decision tree from them.

Decision Tree to Assist in Compliance with the NIH Human Research Protection Program (HRPP)

Question 1. Is the proposed activity Research?

The definition of research used in the NIH HRPP is:

A systematic investigation designed to develop or contribute to generalizable knowledge.

Decision Tree

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Question 1. Is the proposed activity Research?

Compare your proposed activity with the definition of research, and ask yourself the following questions:

- **Is the activity designed to produce generalizable knowledge? In other words, will the information derived from the activity be applicable to other cases?**
- **Will the information be gathered systematically? In other words, will it be arranged so that conclusions can be drawn, and so that others can review those conclusions?**

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Question 1. Is the proposed activity Research?

No

A: HRPP policies related to human subject protections do not apply.

If your answers to the previous questions are NO, then your proposed activity does not meet the HRPP definition of RESEARCH, and the HRPP does not apply to the activity.

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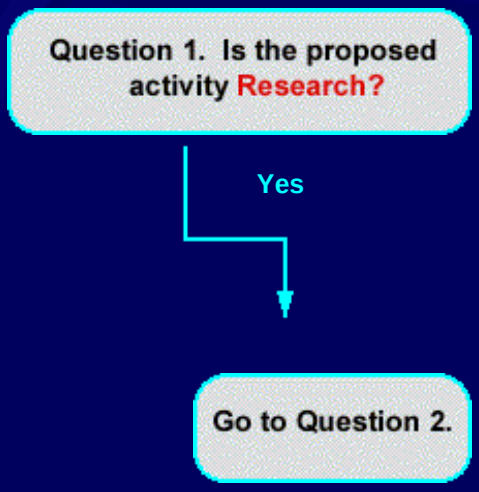

However, if your answers to the previous questions are YES, then the activity IS research and you should proceed with Question #2.

Important Clue: The intent to publish the results of an activity nearly always means that it is research.

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Question 2: Does the research activity involve human subjects?

If the activity is research, then you need to ask, does the research involve any HUMAN SUBJECTS?

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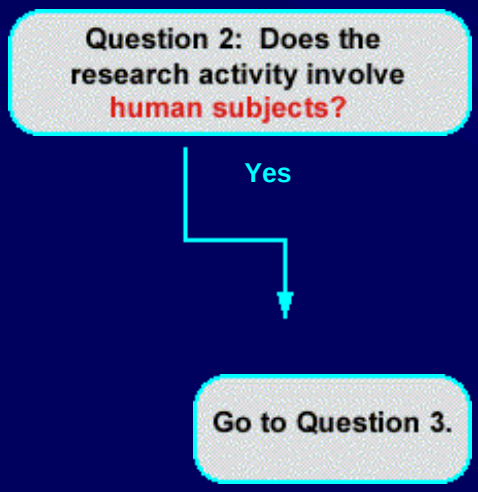

A human subject is involved if:

- **The person is alive and**
- **Data pertaining to the person will be obtained through:**
  - **Intervention (e.g., taking a blood sample).**
  - **Interaction (e.g., taking a medical history).**
  - **A private/confidential source (e.g., from medical records).**

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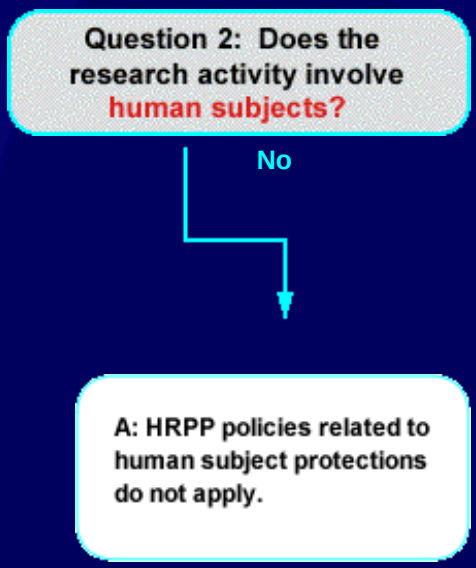

Types of activities often conducted at NIH which are NOT covered by this definition of human subject and are NOT subject to the requirements of the NIH HRPP include research use of: (Note: some of these activities may be subject to other laws or regulations)

- **Samples from deceased individuals and cadaverous tissues.**
- **Established cell lines publicly available to qualified scientific investigators.**
- **Self-sustaining, cell-free derivative preparations including viral isolates, cloned DNA or RNA.**

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Question 2: Does the research activity involve human subjects?

In most cases, the determination of whether a particular research activity involves human subjects is not difficult.

In some cases, however, the issue is not clear. When in doubt, consult with your Laboratory/ Branch/Section Chief or seek advice from OHSR.

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Question 2: Does the research activity involve human subjects?

Yes

Go to Question 3.

If your proposed activity is RESEARCH and HUMAN SUBJECTS will be involved, go to Question #3 of the decision tree.

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Question 3: Is the research exempt from IRB review and approval?

Does the research involving human subjects:

- **Require IRB review and approval?**

OR

- **Is it exempt from IRB review?**

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Question 3: Is the research exempt from IRB review and approval?

There are six categories of research activities involving human subjects that are EXEMPT from the requirement for IRB review and approval.

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Question 3: Is the research exempt from IRB review and approval?

The general rationale behind the six exemption categories is that, although the research involves human subjects, it exposes them only to very small physical, social, or psychological risks that are similar to the risks they take in everyday life, such as applying for a job, answering telephone surveys, tasting food, etc.

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Question 3: Is the research exempt from IRB review and approval?

Adults who engage in these and similar activities can be expected to understand and accept the small risks they are taking.

Therefore, for this reason, they need no special protection offered by IRB review and approval.

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Question 3: Is the research exempt from IRB review and approval?

The most frequently conducted research activity by IRP investigators that is EXEMPT from IRB review is:

The study or collection of existing records or samples (e.g., pathological specimens, data) if these sources are publicly available or if the information is recorded by the investigator so that subjects cannot be identified directly or through identifiers linked to subjects.

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Question 3: Is the research exempt from IRB review and approval?

An example is research analysis of stored human blood samples from which all identifiers have been completely removed.

In this hypothetical example of exempt research, the samples are "existing," (e.g., they are stored in a freezer), and there are no identifiers, therefore, subjects cannot be identified.

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Question 3: Is the research exempt from IRB review and approval?

Note that "identifiers" can include names, initials, social security numbers, patient numbers, or codes. Investigators should be cautious when using such identifiers in their research and should not assume that use of codes renders research samples exempt from IRB review.

The Case Studies Lesson deals with this exemption.

PROTECTING HUMAN RESEARCH SUBJECTS

HUMAN RESEARCH PROTECTION PROGRAM (HRPP)

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Question 3: Is the research exempt from IRB review and approval?

To review other categories of research involving human subjects that are exempt from IRB review and approval, click "Exemptions" below, otherwise, click on the next page button to continue.

EXEMPTIONS

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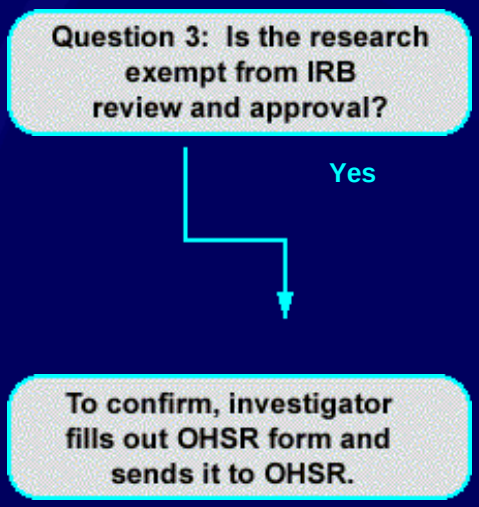

If you believe your research falls into one of the exempt categories, complete the form entitled, "Request for Review of Research Activity Involving Human Subjects" and send it to OHSR. OHSR will respond in writing -- usually within a day or two.

Investigators should not begin research they believe to be exempt until they receive written notification from OHSR.

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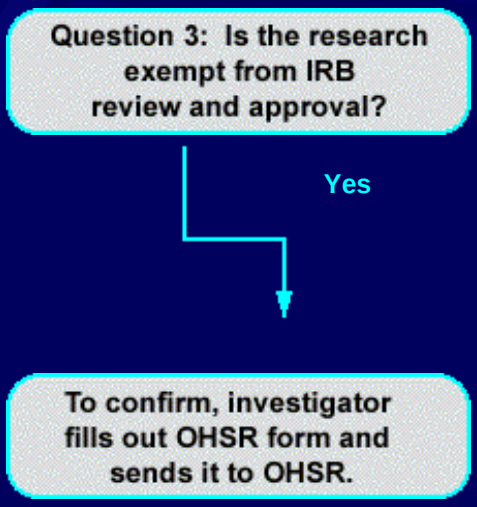

To view the OHSR form, "Request for Review of Research Activity Involving Human Subjects," click the button below.

It is also available through OHSR's web site at http://ohsr.od.nih.gov.

OHSR FORM

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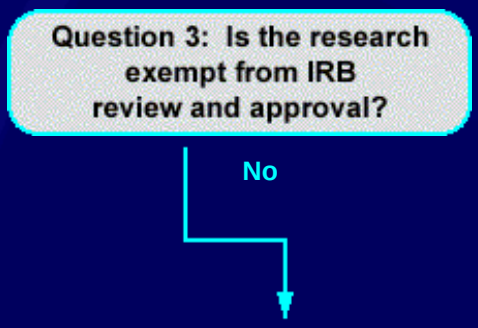

On the last several screens, you reviewed the steps you need to take if you think one of your research activities involving human subjects is EXEMPT from the requirement for prospective IRB review and approval.

Let's complete Question 3 of the decision tree by looking at what you need to do if you think the activity is NOT EXEMPT.

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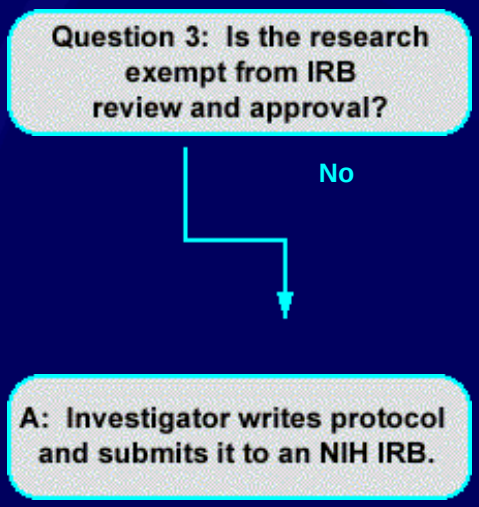

If a research activity is not exempt, then the investigator writes a protocol that describes the proposed research activity and submits the research protocol to the appropriate IRB for review.

An IRB may approve, disapprove, or ask for modification of the protocol.

Research may begin only after IRB and other necessary approvals are obtained.

Research Protocol Format

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The usual format for a research protocol submitted by the Principal Investigator (PI) to an NIH IRB includes:

- **A description of, and scientific rationale for, the proposed research activity.**
- **A REQUIRED section entitled "Human Subject Protections" which includes a discussion of the human subjects protection issues which addresses, at a minimum:**
  - **The risks to subjects.**
  - **All procedures that are experimental.**
  - **The anticipated benefits to subjects, if any.**

Research Protocol Format (Continued)

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- **Subject selection, recruitment procedures, and the anticipated number of subjects.**
- **The proposed consent document and process to be used.**
- **Appropriate additional safeguards if potentially vulnerable subjects are to be enrolled. Potentially vulnerable subjects include the elderly, prisoners, children, cognitively impaired people, or people who are economically or educationally disadvantaged.**

More information on how to prepare a research protocol may be obtained from your Laboratory/Branch/Section Chiefs or the OHSR.

Also, the Clinical Center's publication Protomechanics is available on request from the Clinical Center's Office of Communications (301) 496-2563.

After the protocol is written and the appropriate signatures are obtained, the PI submits it to his/her Institute's IRB.

As of January 2007, the NIH has 12 IRBs.

If you would like a list of the IRBs, press the button below. If not, click the next page button to continue with the lesson.

IRBs

IRBs review research from the vantage point of protecting the rights and welfare of human research subjects. For each new protocol they review, NIH IRBs are required to discuss and document in their minutes that the following criteria are met:

- **The design of the study is consistent with sound scientific principles, ethical guidelines, and legal requirements.**
- **Risks to subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk.**

NIH IRB Review Standards (Continued):

- **Risks to subjects are reasonable relative to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result.**
- **The necessary elements of informed consent have been met and documented and additional elements added when appropriate.**

NIH IRB Review Standards (Continued):

- **Additional appropriate safeguards have been provided if potentially vulnerable subjects are to be studied (e.g., children, prisoners, financially or educationally disadvantaged people).**
- **Subject selection is equitable, with attention to the inclusion of minorities and both genders in study populations so that research findings can be applied to all persons at risk for the disease, disorder or condition under study.**

When presenting a new protocol to a NIH IRB, you should be prepared to address each of these items in your oral presentation.

These NIH IRB review standards may be found at http://ohsr.od.nih.gov/irb/protocol.html.

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In exercising their authority, IRBs may approve, disapprove, or table research protocols. However, IRBs are obligated not to approve any protocol that does not fulfill the NIH IRB Review Standards previously presented.

Most often, the IRB approves a research protocol with required changes, referred to as stipulations. Research may not begin until the stipulations have been met in writing by the PI.

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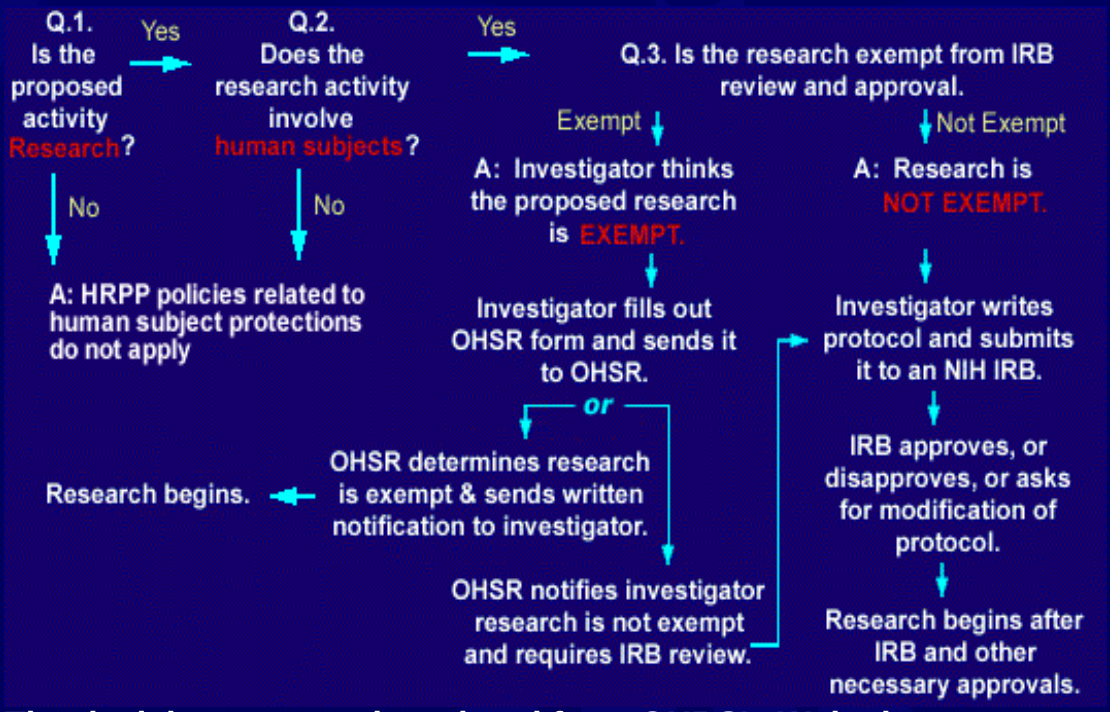
Here is a second look at the entire decision tree for how to proceed with the review and approval of research involving human subjects.



The decision tree can be printed from OHRS's Web site at http://206.102.88.10/ohsrsite/irb/tree.html.

In most cases, research may begin when the IRB-approved protocol receives approvals from your Institute Clinical Director and the Director of the Clinical Center (CC) (if subjects are to be enrolled in the CC) and has been given a protocol number by the CC Office of Protocol Services.

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However, there are some situations in which other authorizations or clearances are required before you begin, such as:

- **Research involving non-medically indicated radiation.**
- **Gene therapy studies.**
- **Certain kinds of collaborative research.**

In the next few screens, we will discuss collaborative research only. Your Laboratory/Branch/Section Chief can give you information on how to obtain authorization for the first two activities.

Special provisions must be made if you intend to collaborate in non-exempt research involving human subjects at sites other than the NIH. These provisions are required because when you collaborate, you accept some measure of responsibility for protecting the rights and welfare of the human subjects involved.

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What constitutes "collaboration" on the part of an NIH investigator?

Collaboration exists if the NIH intramural participant expects "something in return" as a result of having participated in a research activity. "Something in return" could include data, authorship on a publication, samples, or even patent rights.

The NIH views authorship as prima facie evidence of collaboration.

Collaborative activities may include but are not limited to:

- **Collection of specimens.**
- **Visits to institutions to perform research activities or clinical research.**
- **Exchange of information containing personal identifiers.**
- **Preliminary data-collection activities involving human subjects.**
- **Substantive intellectual contributions to research techniques, protocol design, or interpretation of data.**

More remote participation -- such as supplying important reagents, performing laboratory analyses, or analyzing data -- may also constitute collaboration. The degree of review required at the NIH and elsewhere for collaborative research projects depends on the nature and extent of the collaboration. For clarification, check with your Laboratory/Branch/Section Chief, your IRB Chairperson or OHSR (301) 402-3444.

Some general guidelines follow.

In order to collaborate in research where subjects are enrolled at a non-NIH site, you should find out if your collaborator's institution has a Federal Wide Assurance (FWA). Ask your collaborator or, if he/she is not sure, call OHSR.

Most large research hospitals, university medical schools, and other research organizations in the U.S. as well as some foreign institutions with which you are likely to collaborate have FWAs. A list of FWA-holding institutions is available from OHRP and the OHRP web site at http://www.hhs.gov/ohrp.

When you are collaborating with an investigator in an institution with an FWA, research may begin when IRB approval is obtained at the NIH and at your collaborator's institution. (Exceptions to this requirement may be discussed with OHSR.)

Before you begin the research, both you and your IRB must have documentation that your collaborator's IRB has reviewed and approved the protocol.

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When you want to collaborate in research at any domestic site or in foreign countries, you and the NIH need assurance that the rights and welfare of the human subjects involved are appropriately protected. If the site does not have an FWA, an FWA or other OHRP-approved assurance will have to be negotiated.

An assurance is a formal agreement between an institution and the DHHS's Office for Human Research Protections (OHRP) that the institution will abide by the ethical principles of The Belmont Report and 45 CFR 46 in its conduct of a specific collaborative research project.

If an assurance is necessary for your collaborative research study, the Chairperson of your IRB and OHSR will provide information and guidance.

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Summary of Important Points in this Lesson

- The requirements of the NIH HRPP apply to all intramural research involving human subjects, including collaborative activities which enroll subjects at non-NIH sites.
- If you apply the decision tree shown in this lesson, you will be able to analyze whether or not a particular research activity involves human subjects.
- When your research involves human subjects, you should not begin until it has received IRB review and approval OR it is determined by OHSR to be exempt from IRB review.
- The mandate of IRBs is to review research in order to protect the rights and safeguard the welfare of human subjects.

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This ends the Human Research Protection Program of this course. In the Case Studies Lesson, you are given the opportunity to demonstrate how to apply some of the information given in this lesson to actual research activities.

Click on the Menu Button to see more of the course.

Six Exemptions from 45 CFR 46

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as research on:

- **regular and special education instructional strategies; or**
- **effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.**

CLOSE WINDOW

Six Exemptions from 45 CFR 46

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

- **information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers, linked to the subjects; and**
- **any disclosure of the human subjects' responses outside of the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.**

CLOSE WINDOW

Six Exemptions from 45 CFR 46

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior that is not exempt under #2 if:

- **the human subjects are elected or appointed public officials or candidates for public office; or**
- **federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.**

Six Exemptions from 45 CFR 46

4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

CLOSE WINDOW

Six Exemptions from 45 CFR 46

5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

- **public benefit service programs,**
- **procedures for obtaining benefits or services under these programs,**
- **possible changes in or alternatives to those programs or procedures, or**
- **possible changes in methods or levels of payment for benefits or services under those programs.**

Six Exemptions from 45 CFR 46

6. Taste and food quality evaluation and consumer acceptance studies if:

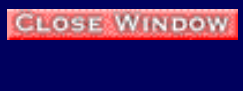
- **wholesome foods without additives are consumed, or**
- **a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.**

Introduction

Research investigators have a fundamental responsibility to safeguard the rights and welfare of the people participating in their research activities.

In addition, our society has decided by law that an objective review of human subjects research by a group of diverse individuals is most likely to protect human subjects and promote ethically sound research.

Therefore, when conducting research involving humans, Federal regulations and the NIH MPA both require prospective and continuing review and approval of the research by a committee called an Institutional Review Board (IRB).



Introduction

IRBs are very important to the conduct of human subjects research at the NIH and other research institutions both inside and outside the U.S.

On the other hand, IRBs have one paramount responsibility: To protect the rights and welfare of human research subjects.

Close Window

Introduction

IRBs take into account national and, when appropriate, international ethical standards of research on a protocol- by-protocol basis. Protecting human research subjects is their primary responsibility.

Protection of the rights and welfare of research subjects is a high priority worldwide. It is reflected in the Nuremberg Code, the United Nations Charter of Human Rights, the Declarations of Helsinki, the guidelines of the World Health

Close Window

Introduction

IRBs at the NIH infrequently disapprove proposed research activities. Instead, they strive to work interactively with research investigators to assure that research design is excellent, that risks are minimized and expected benefits are maximized, and that consent procedures are adequate.

IRB members bring diverse skills, insights, and perspectives to the responsibility of reviewing research activities involving humans.

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Introduction

Although the IRB system is not perfect, conscientious IRBs reassure the American public that the rights and welfare of human subjects are seriously considered by people who do not have a vested interest in the outcome of the research.

By exercising their responsibilities, IRBs promote the protection of human subjects. IRB approval provides a significant affirmation of the scientific and ethical quality of the research, and therefore offers important validation to the research investigator and the research institution.

Introduction

Keep in mind that the application of ethical principles, the Federal regulations (45 CFR 46), and the NIH MPA are intended to balance society's interest in advancing scientific knowledge with its mandate to protect the rights and welfare of human subjects. IRBs' reviews help to achieve this balance.

Experience has shown that sound ethics and good science are compatible. The system, though not perfect, has worked well in the U.S. for more than 30 years.

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PROTECTING HUMAN RESEARCH SUBJECTS

ROLES AND RESPONSIBILITIES

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Dr. Elias Zerhoum
Director, NIH

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- Laboratory Branch/ Section Chiefs
- Principal Investigators
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The offices listed to the right represent the people, officials, and groups who play important roles in implementing the requirements of NIH's HRPP.

Click the Page Forward button above to navigate through a brief description of each of these important responsibilities.

Deputy Director for Intramural Research (DDIR)

Dr. Michael Goltesman

The Deputy Director for Intramural Research (DDIR) is the NIH official who assumes overall responsibility for protecting the rights and welfare of human subjects at the NIH.

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Deputy Director for Intramural Research (DDIR)

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The NIH Federal Wide Assurance (FWA) bears the signature of the DDIR. By signing the FWA, the DDIR has pledged to the Secretary, Department of Health & Human Services (DHHS) (represented by its Office for Human Research Protections –OHRP) that all necessary steps will be taken to assure that IRP personnel will comply with the ethical principles of The Belmont Report, as well as applicable laws and Federal regulations (45 CFR 46), in protecting the rights and welfare of human subjects at the NIH.

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Also, the DDIR has given assurance that IRP research will meet all of its public obligations including the recruitment of minorities and women as research subjects.

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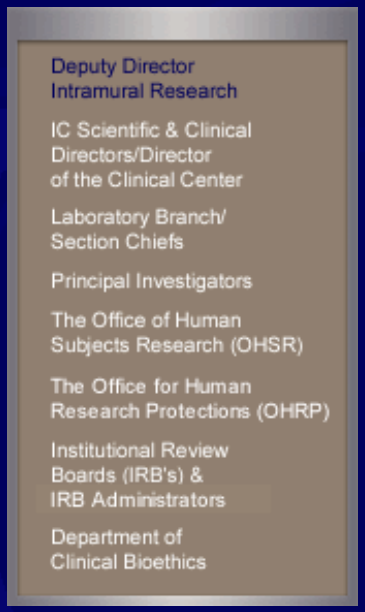
Deputy Director for Intramural Research (DDIR)

The DDIR has delegated to the Institutes the responsibility for assuring that all research protocols are consistent with Institute research objectives, are likely to yield knowledge of importance to the mission of the NIH, and receive substantive pre-IRB scientific review.

The DDIR has other responsibilities, including the appointment of IRB Chairs and members (upon recommendation by IC Clinical and Scientific Directors).



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IC Clinical Directors & Scientific Directors

IC Clinical Directors are responsible for intramural clinical research programs. They review protocols before submission to the IRB and are IC approving officials following IRB review and approval.

Also, they are authorized to suspend or terminate protocols for noncompliance with NIH or CC policy and procedures. Clinical and Scientific Directors recommend appointments of IRB chairpersons and members to the DDIR.

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When research subjects are to be studied at the Clinical Center (CC), the Director of the CC must also review and approve IRB-approved protocols, taking into account the in-house resources necessary to implement them.

This is usually the final review and approval before implementation of a protocol at the CC.

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Director of the Clinical Center

The Director of the CC is authorized to suspend or terminate protocols for non-compliance with NIH or CC policies and procedures.

CC policies and procedures for the conduct of research involving human subjects (e.g. use of ionizing radiation for research purposes) may be found in the Medical Administrative Series (MAS) at http://intranet.cc.nih.gov/mec/mas/index.shtml.

These documents are available from the CC's Office of the Medical Executive Committee Services, telephone: (301) 496-5939.

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Laboratory / Branch / Section Chiefs

Laboratory / Branch / Section Chiefs train and educate IRP investigators in basic and clinical research.

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GLOSSARY

Laboratory / Branch / Section Chiefs

They also:

- **Provide guidance to their research staff and trainees regarding the requirements of NIH's HRPP.**
- **Review and co-sign all "Requests for Review of Research Activity Involving Human Subjects" forms forwarded by their research investigators to OHSR.**

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OHSR FORM

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Laboratory / Branch / Section Chiefs

They also:

- **Recommend for IRB review all proposed research involving human subjects to be conducted by research staff of their unit.**
- **When making this recommendation, they are expected to take into account scientific merit, ethical considerations, and relevance of the research to the program and the mission of the NIH.**

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Principal Investigators

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A complete overview of the responsibilities of a Principal Investigator (PI) is given in your IRB's Standard Operating Procedures (for more information contact your IRB Administrator). A brief review is given here.

The PI's knowledge and skills are critical to the success of a research protocol. Therefore, before undertaking a PI's responsibilities you should, at a minimum, familiarize yourself with the requirements of the NIH's HRPP, the relevant Clinical Center (CC) policies, and seek the advice and guidance of experienced investigators.

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GLOSSARY

Principal Investigators

The Principal Investigator:

- **Designs the research study.**
- **Writes the protocol.**
- **Submits the protocol to the proper NIH IRB for initial review and approval.**
- **Complies with all IRB decisions and stipulations.**

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Principal Investigators

The Principal Investigator also:

- **Is responsible for the conduct of the protocol, including rigorous adherence to sound scientific procedures and accepted ethical principles.**
- **Submits all required forms/information to the IRB for its continuing review of the protocol.**
- **Reports promptly to the appropriate NIH IRB and others any unanticipated problems involving risks to subjects or others, or unexpected serious harm to subjects.**

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Principal Investigators

Finally, the Principal Investigator:

- **Submits to the IRB proposed amendments to previously approved research.**
- **Complies with all requirements of the Food and Drug Administration when using investigational drugs, investigational devices, biologics, or other regulated test articles.**
- **Reports promptly to OHSR and the appropriate NIH IRB any serious or continuing non-compliance with the requirements of 45 CFR 46, the NIH HRPP, or the determinations of the IRB.**

The CC requires all PI's to complete a computer-based-training program and pass a written examination.

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The Office of Human Subjects Research (OHSR)

The Office of Human Subjects Research (OHSR) reports to the Deputy Director for Intramural Research (DDIR). It is located in Building 10, Room 2C-146.

OHSR has a number of responsibilities, but its most important one is to provide the intramural research community with information, education, and guidance with respect to the ethical, regulatory, and procedural requirements to be followed in research involving human subjects.

(continued)

The Office of Human Subjects Research (OHSR)

OHSR works closely with the NIH's IRBs to promote their mandate to protect human subjects, and consults with investigators, upon their request, to help identify and resolve ethical and regulatory issues associated with the design and conduct of their research activities.

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The Office of Human Subjects Research (OHSR)

For example, if you plan to do research involving children, there are special ethical and legal requirements which you need to take into account when designing the research and writing your protocol.

You may request a consultation by calling OHSR at (301) 402-3444.

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The Office of Human Subjects Research (OHSR)

OHSR plans, organizes, and conducts educational activities for members of the intramural research community.

If you would like to arrange an educational program for your Laboratory, Branch, or Section, or request educational materials, please call OHSR at (301) 402-3444.

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The Office of Human Subjects Research (OHSR)

OHSR helps the DDIR and the IRP formulate policies and procedures which are consistent with ethical norms, Federal regulations, and the other requirements of the NIH HRPP.

Upon request by the DDIR, OHSR assists in the conduct of inquiries and/or investigations concerning non-compliance on the part of intramural researchers with the policies and procedures of the NIH's HRPP.

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Office for Human Research Protections (OHRP)

OHSR and the Office for Human Research Protections (OHRP) are NOT the same office. OHSR is an office at the NIH that serves researchers in the NIH IRP. On the other hand, OHRP is an office in the Department of Health and Human Services (DHHS). OHRP was formerly called the Office for Protection from Research Risks (OPRR). The OHRP has responsibility, delegated by the Secretary of the Department of Health and Human Services (DHHS), for promulgating, implementing, and overseeing regulations for the protection of human subjects (45 CFR 46) when research involving human subjects is conducted or funded by any component of DHHS.

OHRP coordinates the oversight of human subjects protection within other Federal departments and agencies.

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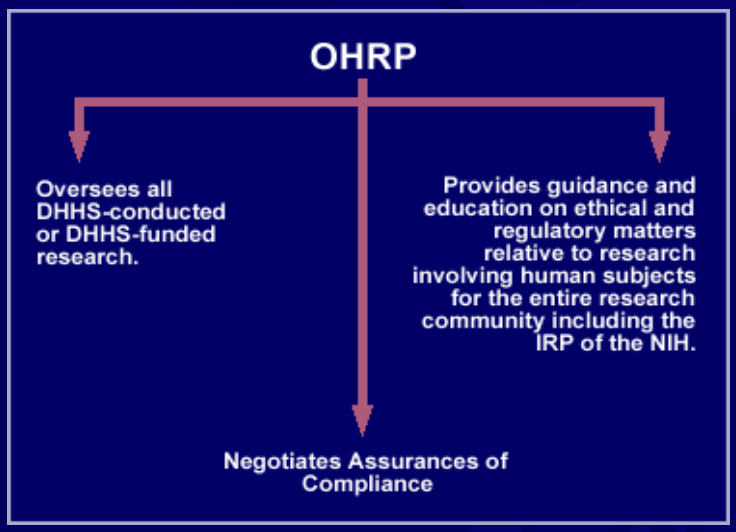

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Office for Human Research Protections (OHRP)

DHHS regulations for the protection of human subjects require each institution that conducts research involving human subjects to describe, in detail, the procedures it will use to protect the rights and welfare of the human subjects.

Each institution prepares a document that describes these procedures.

The document is called an "Assurance of Compliance," commonly referred to as an "assurance."

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There are several kinds of assurances covering research at different institutions or sites.

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The Federal Wide Assurance (FWA), which serves as the NIH intramural guide to protecting human subjects, is the most comprehensive kind of assurance approved by OHRP.

Most major medical centers in the U.S. and abroad have FWAs. As of January 2006, OHRP reported that it has approved 9,350 assurances with entities in the United States and abroad.

When an OHRP-approved assurance is in place, the institution must conduct its research in keeping with the terms and conditions of that assurance.

For questions concerning assurances contact your IRB chair or OHSR.

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Office for Human Research Protections (OHRP)

OHSR serves as the liaison office with OHRP on all matters dealing with the NIH FWA.

Therefore, OHSR is the office to contact with any questions regarding the applicability or implementation of NIH requirements for research involving human subjects.

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Institutional Review Boards (IRBs)

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Some of the IRBs' responsibilities were presented in the Course Introduction, and in the lesson entitled NIH Human Research Protection Program.

You can review the Course Introduction by clicking the button below and the lesson on the NIH Human Research Protection Program is available from the Main Menu.

Note: The Course Introduction will launch in a new browser window. Once you have completed reviewing the course intro, close the browser window to return to this location.

COURSE INTRO

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Institutional Review Boards (IRBs)

Each IRB has a IRB Administrator who assists the IRB Chairperson and members with various administrative and record-keeping procedures, including liaison with the Clinical Center Office of Protocol Services.

IRB Administrators also provide guidance to Principal Investigators concerning particular Institute requirements for protocol review.

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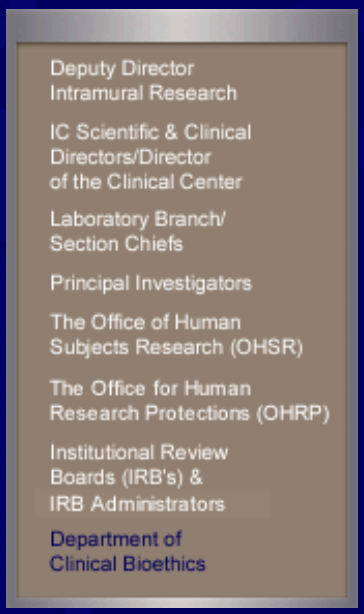
The Department of Clinical Bioethics, which is part of the Office of the Director of the Clinical Center, is designed to further the NIH's commitment to the highest standards of biomedical research and patient care.



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Department of Clinical Bioethics

Staff of the Department of Clinical Bioethics:

- **Are members of each of the NIH's IRBs.**
- **Assist in discussions of ethical issues, such as research design, benefits and risks, selection of subjects, and informed consent.**
- **Offer investigators a broad range of consultation services.**
- **Assist in writing and editing informed consent documents.**

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Department of Clinical Bioethics

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Staff of the Department of Clinical Bioethics:

- **Promote high standards of patient care.**
- **Often participate in patient care rounds.**
- **Provide educational and other services for the CC, Institutes, staff, patients, families, and the general public.**

Department of Clinical Bioethics staff can be reached by calling (301) 496-2429.

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PROTECTING HUMAN RESEARCH SUBJECTS

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This concludes

the Roles and Responsibilities

Section of this program.

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Case Studies Lesson

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This lesson presents several situations which you may encounter as a researcher at the NIH. The point is to demonstrate how the policies and procedures of the NIH HRPP are applied in particular situations, and when it is advisable for you to seek assistance in making your decisions.

Case Studies Lesson

DECISION TREE

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In each of these cases, you play the role of an intramural investigator being presented with a situation in which you have to make a decision about how to proceed with the research.

If you want to review the decision tree (discussed in the Human Research Protection Lesson) to assist you in decisions, click on the Decision Tree button above.

Case Study One

DECISION TREE

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GLOSSARY

Your colleague at another institution calls you on the phone to ask if you will analyze some human blood samples.

She says that the samples were collected from cancer patients and, currently, are stored in her laboratory freezer.

You are very interested in doing the research analyses. She says she can send them to you by overnight delivery.

PROTECTING HUMAN RESEARCH SUBJECTS

CASE STUDIES

Case Study One

DECISION TREE

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Click on the choice that you think is the best course of action.

1. **You encourage your colleague to send the samples as soon as possible. You plan to begin analyzing them as soon as they arrive.**
2. **You ask her for more information about the samples.**
3. **You say you will consider the matter and call her back after seeking advice, but you are not sure whom to ask for advice.**
4. **You tell her not to send the samples because you are not permitted to analyze them unless you first prepare a research protocol and get IRB approval for it. The process is too cumbersome and complicated.**

Case Study One

DECISION TREE

Choice A

You encourage your colleague to send the samples as soon as possible. You plan to begin analyzing them as soon as they arrive. This is not a good choice.

If you make this choice, based solely on the information presented, you will run the risk of:

- **Violating the rights of the subjects**
- **Being in non-compliance with the requirements of the Federal regulations (45 CFR 46) and the NIH MPA.**

The research that your colleague is asking you to do -- research analyses on previously collected human samples -- is considered research with human subjects and is covered under the NIH MPA.

Before you agree to analyze the samples, you need more information about them, therefore the best answer is B. (You ask for more information about the samples).

Case Study One

Choice C

DECISION TREE

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GLOSSARY

You say you will consider the matter and call her back after seeking advice, but you are not sure whom to ask for advice.

Certainly it is acceptable for you to delay giving your colleague an answer until you get more information concerning what the NIH requires of you when you collaborate in research.

For advice you may contact the chair of your institute's IRB or call OHSR at 301-402-3444.

Case Study One

Choice C

If you are unsure what to do, call or visit the OHSR

(Building 10, Room 1 C-116, telephone (301) 402-3444) for advice.

You may also discuss it with your Lab/Branch/ Section Chief or the Chairperson of your NIH IRB.

Case Study One

Choice C

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GLOSSARY

If you had called the OHSR to discuss this case, you would have been asked for more information.

Therefore the best answer to the case study is B.

(You ask her for more information about the samples).

Case Study One

Choice D

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You tell her not to send the samples because you are not permitted to analyze them unless you first prepare a research protocol and get IRB approval for it. The process is too cumbersome and complicated to bother with.

You may or may not need IRB review and approval. You need more information for your collaboration.

Case Study One

Choice D

DECISION TREE

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However, based solely on the information given initially by your colleague, you cannot decide if this research needs IRB review and approval.

To make a determination you need more information.

Therefore, the best answer is B.

(You ask her for more information about the samples).

Case Study One

Choice B

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You ask her for more information about the samples.

This is the best choice.

Case Study One

Choice B

DECISION TREE

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You need more information before you can decide how to proceed. The research that your colleague is asking you to do -- research analyses on previously collected human samples -- is considered research with human subjects.

Therefore you must decide, based on the information you get from your colleague, whether or not your research analyses of these blood samples require NIH IRB review and approval before you begin.

Case Study One

Choice B

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Even though you have no contact with the people who provided these blood samples, you still have a responsibility to respect the rights and safeguard the welfare of the human subjects and to make sure that your research activities are in keeping with the NIH HRPP.

Therefore, before you begin, you must decide if your research:

1. **Is exempt from the requirement for IRB review and approval, or**
2. **Requires IRB review and approval.**

Case Study One

DECISION TREE

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Based on your conversations with your colleague, and your understanding of the requests of the NIH HRPP, you realize there are several possible courses of action concerning these blood samples.

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Possibility #1

You and your colleague decide that she will send you the samples with no identifiers that can be linked to a living human being, and that neither of you will contact subjects based on the results of your analyses.

In this circumstance, the research is exempt from the requirement for IRB review and approval.

Possibility #1

Samples Sent to You Without Identifiers

In this circumstance, it would be correct for you to make a preliminary judgment that this research is exempt.

However, in the NIH Intramural Research Program, only OHSR is authorized to determine whether a research activity is exempt from the requirement for IRB review and approval.

Possibility #1

Samples Sent to You Without Identifiers

Therefore, you should complete the OHSR form entitled, "Request for Review of Research Involving Human Subjects" and send it to OHSR for final determination of exempt status.

If OHSR agrees that it is exempt, you will be sent notification by fax, usually within a day or two, after which you may begin your research.

PROTECTING HUMAN RESEARCH SUBJECTS

CASE STUDIES

Case Study One

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Possibility #1

Samples Sent to You Without Identifiers

If you would like to see the completed OHSR form for this possibility, please press the button below, otherwise, click on the next page button to continue.

COMPLETED FORM

Case Study One

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Possibility # 2

Donors are Deceased

Your colleague tells you that the samples contain identifiers but the cancer patients who provided the blood are all deceased. In this circumstance, the requirements of the NIH HRPP do not apply to your research.

However, because local or state laws may apply to the use of organs, tissues, and samples from deceased individuals, you should discuss the research with your Laboratory / Branch / Section Chief.

You may also call OHSR for assistance (301) 402-3444

Possibility # 3

Samples Sent to You With Identifiers

The samples will be sent to you with identifiers that will allow you or your colleague to identify subjects. In some cases, your colleague may intend to contact the people based on the results of your analyses.

Even though you have no direct contact with the blood donors, you will, by your analyses, obtain private information about them and send it to your colleague. Your colleague can link that information to research subjects who may be unaware that this private information is being obtained.

Possibility # 3

Samples Sent to You With Identifiers

In this circumstance, the research is not exempt. You must submit a protocol to your NIH IRB for review and approval before you begin.

In many cases, when you want to do this kind of research, the "protocol" may take the form of a memo to your NIH IRB Chairperson.

This protocol would describe the research and address any risks or other issues related to the protection of the human subjects.

Case Study One

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Possibility # 3

Samples Sent to You With Identifiers

Once the Chairperson reviews your protocol, he/she may approve the research or refer it for review by the entire IRB.

Either way, if you provide the IRB with sufficient information, this need not be a lengthy process.

Possibility # 3

Samples Sent to You With Identifiers

The reason for IRB review in this instance is clear.

The research carried out by you and your colleague involves confidential information about particular people (i.e., the donors of the samples) that may infringe their privacy.

IRB review and approval is important to make sure, before the research begins, that the rights of the subjects have been given serious consideration and are protected.

Before you begin research analyses of existing human samples (i.e., frozen / stored blood / tissue specimens) or existing private data about humans . . .

ASK YOURSELF:

- **Do the samples / data contain identifiers (codes, initials, etc.) that either I or someone else could link to a living individual?**
- **If the answer is "yes" then your proposed activity is considered research with human subjects and you need IRB review and approval before you begin.**

Case Study Two

Let's analyze the case presented in the Course Introduction in more detail.

Dr. B., an oncologist in an economically-developing country, is conducting a controversial trial to develop a vaccine against gastric cancer which is highly prevalent in his country.

Case Study Two

You have a long, professional association with Dr. B. He was a research fellow in your NIH laboratory; you have collaborated on several research projects, and you are co-authors on a number of publications.

Case Study Two

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GLOSSARY

He called and asked you to perform some research analyses of blood samples that will be drawn from subjects in the proposed vaccine trial and to help with the data evaluation.

He suggested that you be identified as a co-author on relevant research publications. You want very much to work with him on this project.

Case Study Two

Choose the best course of action:

1. You ask him to write a research protocol for you to review because you must get NIH IRB approval before you collaborate in this research.
2. You are not sure what to do. You want advice but are not sure whom to ask.
3. You tell him you want to work with him on the research project and you agree to have him send the first batch of blood samples to you next week.

Click on the best choice.

Case Study Two

Choice B

DECISION TREE

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You are not sure what to do. You need advice but are not sure whom to ask.

For more information about the NIH's policies and procedures related to collaborative research, you can ask your Laboratory/ Branch/ Section Chief, the Chairperson of your NIH IRB, or contact OHSR (301) 402-3444.

Case Study Two

Choice B

DECISION TREE

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GLOSSARY

Before you collaborate in this research project, you must have the protocol reviewed and approved by your NIH IRB, and so the most appropriate answer is A (you ask him to write a research protocol for you to review, because you will need to get NIH IRB approval before you get involved in the research).

Case Study Two

Choice C

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Choice C. You tell him you want to work with him on the research project and you agree to have him send the first batch of blood samples to you next week.

This is not a good choice.

Case Study Two

Choice C

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If you make this choice and proceed with the research, you will run the risk of:

1. **Violating the rights of the subjects,**
2. **Being in non-compliance with the requirements of the Federal regulations (45 CFR 46) and the NIH MPA.**

Therefore, the most appropriate answer is A (you ask him to write a research protocol for you to review, because you will need to get NIH IRB approval before you get involved in the research).

Case Study Two

Choice A

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You ask him to write a research protocol for you to review, because you must get NIH IRB approval before you collaborate in this research.

This is the best course of action.

Case Study Two

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When you collaborate in research activities that involve humans at sites other than the NIH, you and the NIH accept some measure of responsibility for protecting the rights and welfare of human subjects at the collaborating institution.

Even though you will not have any direct contact with the people who are the subjects of this research, the NIH expects you to know and follow the requirements of the NIH MPA related to the protection of human subjects wherever collaborative research activities occur.

Case Study Two

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Clearly, in this case, your colleague is asking you to collaborate in research involving humans in a foreign country because you will provide guidance on the study design, analyze blood samples from identifiable people, and co-author research publications.

Therefore, in keeping with the requirements of the NIH HRPP, you must have the research protocol reviewed and approved by your NIH IRB before you may begin.

To review the NIH definition of collaborative research, click here.

Otherwise, click on the next page button to continue.

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Most large research institutions in the U.S. have FWAs and a substantial number of institutions in foreign countries have them as well.

If you want to collaborate in this research project you should make sure your collaberating institution has an FWA, or another OHRP-approved assurance, or is willing to negotiate with OHRP or an assurance before the research begins. Research may not begin without an OHRP-approved assurance.

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The assurance is a formal agreement between Dr. B's institution and the Office for Human Research Protections (OHRP) that in the conduct of this collaborative vaccine study, the institution and its researchers will abide by the ethical principles of The Belmont Report and the Federal regulations (45 CFR 46).

Case Study Two

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The assurance requires that Dr. B's institution must either already have an IRB or organize one to provide prospective and continuing review of the research.

The on-site review is important because local IRBs, particularly in foreign countries, are familiar with the laws and cultural background of the local populations.

Case Study Two

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The decision about whether an assurance is necessary is usually made by the NIH IRB at the time that it reviews a collaborative research protocol.

If one of your protocols requires negotiation of an assurance, the Chairperson of the NIH IRB or the staff of OHSR will provide guidance and assistance.

Case Study Two

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Important Points of Case Study Two

- **When IRP investigators collaborate in research, they and the NIH accept some measure of responsibility for protecting the rights and welfare of human subjects at the collaborating institution(s).**
- **In all research involving humans, including collaborative activities, IRP investigators are expected to follow the requirements of the NIH HRPP.**
- **IRP investigators should be familiar with the NIH's guidelines on what constitutes "collaborative research" and the requirements of the NIH HRPP.**

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This concludes the Case Study Lesson of this course.

Click the Main Menu button to see more of the course.

Definition of Collaborative

The NIH considers a research activity to be collaborative if the NIH intramural participant expects "something in return" as a result of having participated in the research.

"Something in return" could include data, authorship on a publication, samples, or even patent rights.

The NIH views authorship as prima facie evidence of research collaboration.

CLOSE WINDOW

Definition of Collaborative

Some Examples of Collaborative Research Activities Are:

- **Collection of human specimens for research purposes**
- **Visits to institutions to perform research involving human subjects**
- **Collection of data about human subjects**
- **Exchange of private information about people that contains personal identifiers**
- **Substantive intellectual contributions to research techniques, protocol design, or interpretation of data**

CLOSE WINDOW

Definition of Collaborative

More remote participation -- such as supplying important reagents, performing laboratory analyses, or analyzing data -- may also constitute collaboration, especially if it is part of an informal or formal collaborative agreement (i.e., documented by a letter of collaboration or a CRADA).

The first thing you should do is request that your collaborator send you a research protocol.

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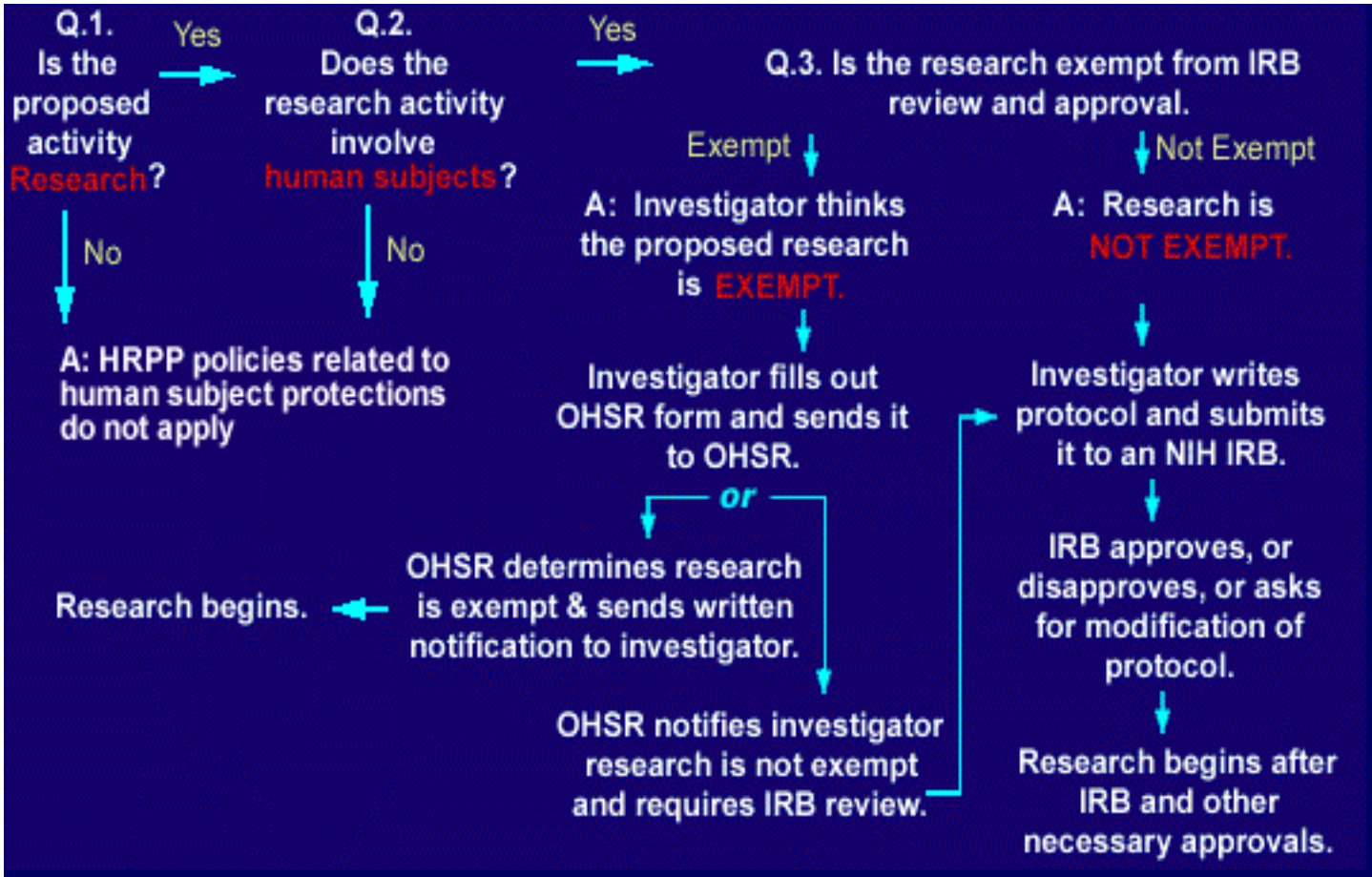

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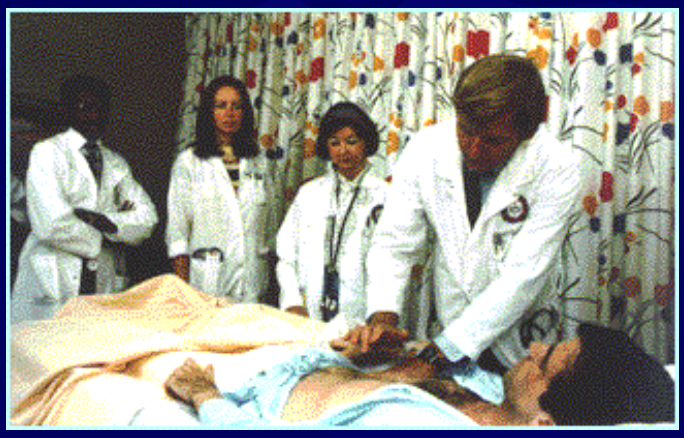
Course Summary



You may not remember everything in this course but there are many people who can help you if you have questions about your research activities.

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Where to go for HELP and INFORMATION

If you need HELP deciding whether your research activities involve human subjects:

- **Ask your Laboratory/Branch/Section Chief.**
- **Discuss your proposed research with your NIH IRB Chairperson, and/or Call OHSR at (301) 402-3444.**
- **If you want a copy of the NIH's HRPP or FWA:**

  Ask your Laboratory/Branch/ Section Chief, or Call OHSR at (301) 402-3444.

Where to go for HELP and INFORMATION (Continued)

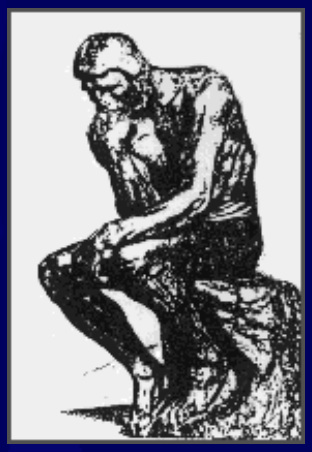
If you need ASSISTANCE writing a research protocol:

- **Ask your Laboratory/Branch/Section Chief.**
- **Call the Office of Clinical Center Communications to obtain a copy of "Protomechanics" at (301) 496-2563.**
- **Call OHSR at (301) 402-3444.**

Where to go for HELP and INFORMATION (Continued)

If you need HELP planning a research study which involves unusual, challenging, or complex ethical or regulatory considerations:

- **Ask your Laboratory/Branch/ Section Chief.**
- **Discuss it with your NIH IRB Chairperson.**
- **Call OHSR at (301) 402-3444.**
- **Call the Department of Clinical Bioethics (301) 496-2429.**



Where to go for HELP and INFORMATION (Continued)

If you would like educational materials, or want to arrange an educational program concerning research involving human subjects:

- **Call OHSR at (301) 402-3444.**
- **You may visit the OHSR Web site at http://ohsr.od.nih.gov**

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PROTECTING HUMAN RESEARCH SUBJECTS

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You have completed the didactic part of this course. If you took this course because the NIH requires it, you must now complete a brief evaluation to record your completion of the course.

Once you complete the evaluation, you will have the opportunity to:

- **View and print a certificate of course completion**
- **View and print your responses to the evaluation**
- **View links to documents mentioned in the course**

To initiate the evaluation process, click Complete Evaluation.