# RESEARCH ETHICS & REVIEW BOARD

## Research Definition

**The Department of Health and Human Services (HHS) defines research at 45 CFR 46.102(d) as follows:**

*Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Activities that meet this definition may be funded or unfunded, or may be conducted as a component of another program not usually considered research. For example, demonstration and service programs may include evaluation components, which constitute research activities under this definition.

There are two key elements to this definition that must BOTH be met for the project to be classified as research.

First, the project must involve a systematic investigation. *Systematic investigation* involves a prospective plan which incorporates (a) the organized collection of quantitative and-or qualitative data, or biological specimens, and (b) analysis (or anticipation of analysis) of those data or specimens to answer a question or questions.

Second, the primary reason for conducting the project must be to develop or contribute to generalizable knowledge. *Generalizable knowledge* includes one or more of the following:

- The data is geared for scholars, practitioners, and-or researchers within a specified field of study
- Results of the study are presented either by presentation and-or publication in order to illuminate some topic or issue within one's field of study
- Results from the study are applied to some population in addition to the sample
- The study's results can be replicated by others
- The study provides input into some field of study

Some projects may include systematic investigation (e.g., a Quality Improvement [QI] project aimed at improving local systems of care), but have no intent to generate generalizable results. Likewise, some projects have results worth sharing through publication or presentation, but include no element of systematic investigation. Those projects are more accurately classified as *education*, not research. In fact, the goal of most educational activities is to spread or transfer knowledge; however, this does not automatically imply that the activity involves systematic investigation. If a project has only ONE of the key elements in the definition of research, then the activity is NOT research (adapted from University of Michigan).

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**HHS regulations define *human subject*s at 45 CFR 46.102(f) as follows:**

*Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

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

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

*Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be **individually identifiable** (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects (bolding added for emphasis).

For purposes of this document, *coded* means that:

1. Identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and
2. A key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

## Understanding How to Apply Research Definition

Precedent and practice have established the principle that certain kinds of activities that might be called “human participant research” do not require review for the protection of human participants. The following kinds of activities do not require such review:

- Accepted and established service relationships between professionals and clients where the activity is designed solely to meet the needs of the client;
- Research using only historical documents; and
- Research using only archaeological materials or other historical or pre-historical artifacts.

Note, pilot studies, pre-tests, and other "preliminary" investigations are considered research, and must be reviewed unless they fall into one of the excluded categories listed above.

Classroom activities may include instructing students in research methodologies and techniques. If the activity is designed solely to teach students research techniques or methodology and not to develop or to contribute to generalizable knowledge, it is not considered to be research. However, if students will practice research methodologies on human beings, they should be instructed in the ethical conduct of such activities and should be advised to obtain informed consent from their potential participants.

Quality improvement and quality assurance activities conducted solely for the intent of maintaining or improving quality of services provided by an institution, likewise, are not considered research activities. However, if the data collected are generalizable and are to be shared outside of the institution through discussion, presentation, or publication, the activity qualifies as research. Sometimes, data from a quality improvement or quality assurance activity become of interest to the external community after they have been analyzed. In these cases, the research use of the data collected for another purpose must be reviewed.

## Exemption

Research activities in which the only involvement of human participants will be in one or more of the following categories are considered exempt. Each of the categories is quoted from **45 CFR, Part 46.101.B**, and is followed by an explanatory paragraph.

*"Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (a) research on regular or special education instructional strategies, or (b) research on the effectiveness of or on the comparison among instructional techniques, curricula, or classroom management methods."*

**Explanation:** The purpose of this category is to exempt research on educational practices, in an educational institution. This category does not extend to research conducted in a school setting but not related to the instruction in that institution. For example, an evaluation of two methods of fourth grade classroom instruction in a local school district would qualify as exempt research. A sociometric survey of children's preferences for playmates in the same school, involving the same children, would not qualify as exempt research. As the example indicates, research on minor students can be exempt if it is educational research in the sense intended here.

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

A. *Information obtained is recorded in such a manner that the human participants can be identified, directly or through identifiers linked to the participants; and*
B. *Any disclosure of the participant's responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation."*

**Explanation:** "Educational tests" refers to standardized tests used for educational purposes, such as a scholastic achievement test. It does not refer to personality tests or clinical evaluations. Survey or interview studies qualify as exempt unless the participants can be identified from the records, and there are risks to the participants due to the sensitive nature of their responses.

Studies of publicly observable behavior are exempt from Federal regulations unless there are potential risks of the type described and the data are recorded in a way that could be used to identify participants.

Massachusetts College of Art and Design interprets "public behavior" to mean behavior that is apparent to an unconcealed observer, without the use of any special or surreptitious equipment, such as binoculars, special microphones, or recording devices.

*"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 paragraph (2)(b) of this section, if:*

C. The human participants are elected or appointed officials or candidates for public office; or
D. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

**Explanation:** *"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 the participants cannot be identified, directly or through identifiers linked to the participants."*

**Explanation:** Historical, literary, and journalistic research of the type described earlier as being excluded typically would also be described by point D.

Situations arise in which records may be excerpted from a data source that does contain identified, sensitive information, but are provided to the investigator without identifiers. For instance, physicians might be asked to provide case summaries without identifiers. Such studies may be exempt, providing that the person excerpting the records already has authorized access to them for research purposes, and the investigator has no access to the original records.

“Existing” means that the data are “on the shelf” at the time the researcher develops a proposal for their use. Use of data not already on the shelf is not eligible for exemption.

*“Research and demonstration projects which are conducted by or subject to the approval of the US Federal department or agency heads, and which are designed to study, evaluate or otherwise examine: (a) public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; or (c) possible changes in or alternatives to those programs or procedure; or (d) possible changes in methods or levels of payment for benefits or services under those programs.”*

**Explanation:** The “US Federal department or agency heads” referred to are federal, not state, local, or university. This category of exempt research refers to activities sponsored by federal agencies to evaluate their own benefit or service programs.

“Taste and food quality evaluation and consumer acceptance studies, (a) if wholesome foods without additives are consumed or (b) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.”

## The following five categories of research are not exempt, and always require review.

1. Research involving Prisoners
2. Studies of pregnant women where the focus of the research is on pregnancy and/or the fetus
3. Research on fetuses in utero

4. Research on minor children unless the research qualifies as educational research in the sense of items 1 and 2 above, or where the research does not involve direct interaction with the child
5. Research using non-public records

## Expedited Research

Research activities involving “no more than minimal risk” and in which the only involvement of human participants will be in one or more of the following categories may be reviewed using an expedited procedure by the Institutional Review Board Chair. Each of the categories is quoted by the Federal regulations at 45 CFR, part 46, and followed by an explanatory paragraph.

> *“Collection of data from voice, video, digital or image recordings made for research purposes”*

**Explanation:** Because recordings made of participants are de facto identifiable, research involving these techniques which would otherwise be exempt are eligible for minimal risk review using the expedited procedure. Such studies will be approved if the researcher outlines appropriate mechanisms to minimize the risks of invasion of privacy and breach of confidentiality.

> *“Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: some research in this category may be exempt from the HHS regulations, 45 CFR, Part 46.101 (b)(2) and (b)(3), for the protection of human participants. This listing refers only to research that is not exempt.)”*

**Explanation:** Much behavioral research that does not qualify from exemption may be reviewed as minimal risk using the expedited procedure. This category is designed to accommodate research activities that pose no more than minimal risk to participants and that are not eligible for exemption. Please note that this category now includes minor participants.

> *“Medical research with minimal risk:*

a. Clinical studies of drugs and medical devices only when either of the following conditions is met:

*Research on drugs for which an investigational new drug application (21 CFR, Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for minimal risk review.)*

Research on medical devices for which:

i. an investigational device exemption application (21 CFR, Part 812) is no required; or
ii. the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

*b. "Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:*

*i. From healthy, nonpregnant adults who weigh at least 110 pounds. For these participants, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or*

*ii. From other adults and children, considering the age, weight, the health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week."*

**Explanation:** This category allows minimal risk review of activities involving invasive blood draws from healthy normal participants and from non-healthy, pregnant, and minor participants within certain limits. Unless the researcher can demonstrate that infants and other minors would undergo a blood draw as a part of a "routine" physical examination, blood draws from healthy minors will not be reviewed as minimal risk using the expedited procedure.

*c. Prospective collection of biological specimens for research purposes by noninvasive means.*

*Example: Hair and nail clippings.*

> *d. "Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for minimal risk review. This includes studies of cleared medical devices for new indications."*

*Examples:*

> *Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the participant or an invasion of the participant's privacy;*
> *Weighing or testing sensory acuity;*
> *Magnetic resonance imaging;*
> *Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography;*
> *Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual."*

**Explanation:** The examples listed are neither exclusive nor exhaustive. This category may be applied to research involving prospective collection of data for research purposes using non-invasive methods in addition to those listed as examples.

> *"Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations, 45 CFR, Part 46.101 (b)(4), for the protection of human participants. This listing refers only to research that is not exempt.)"*

**Explanation:** This category allows the prospective use of data collected for non-research purposes. Data include information from medical records, insurance claim data, educational testing data, and other non-public information in identifiable form. Data set linkages could be considered in this category. The researcher must

demonstrate that sufficient measures will be used to protect the confidentiality of the data to minimize the risk to participants of inadvertent disclosure.

> *"Continuing review of research previously approved by the convened IRB as follows:*
>
> a. where
>
> > *i. the research is permanently closed to the enrollment of new participants;*
> > *ii. all participants have completed all research-related interventions; and*
> > *iii. the research remains active only for long-term follow-up of participants; or*
>
> *b. where no participants have been enrolled and no additional risks have been identified; or*
> *c. where the remaining research activities are limited to data analysis."*

**Explanation:** Researchers who wish to have their applications for continuing review of projects previously reviewed by the IRB will have to demonstrate that the above conditions have been met.

*"Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories 2 through 5 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified."*

**Explanation:** This category applies to situations in which the full IRB conducts a continuing review of a study and determines that the following activity poses only minimal risks.

## Full Review

All research conducted by faculty, staff, or students that is not determined to be exempt and is not eligible for expedited review must be discussed by the full board at a scheduled meeting.

## Background

### History of Ethics

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

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

As a direct result of the trial, the Nuremberg Code was established in 1948, stating that "The voluntary consent of the human participant is absolutely essential," making it clear that participants should give consent and that the benefits of research must outweigh the risks.

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

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

U.S. Senate hearings followed and in 1962 the so-called "Kefauver Amendments" to the Food, Drug and Cosmetic Act were passed into law to ensure drug efficacy and greater

drug safety. For the first time, drug manufacturers were required to prove to the FDA the effectiveness of their products before marketing them.

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

Issues addressed in the Declaration of Helsinki:

- Research with humans should be based on the results from laboratory and animal experimentation
- Research protocols should be reviewed by an independent committee prior to initiation
- Informed consent from research participants is necessary
- Research should be conducted by medically/scientifically qualified individuals
- Risks should not exceed benefits

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

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

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

**Radiation Experimentation and Human Participant Abuses:** Another example of abuses of human participants occurred during World War II and the early cold war when U.S. officials studied the effects of radiation through experiments on hospital patients, pregnant women, retarded children, and enlisted military personnel. Few of the participants of the experiments gave informed consent; most had no knowledge that they were being subjected to radioactive materials. Manhattan Project officials authorized the wartime experiments to establish health and safety standards for the thousands of workers in atomic bomb plants. After the war, as the cold war deepened, officials justified expanded study of the effects of radiation on the grounds of national security. Following congressional investigations, numerous official reports, scholarly studies, and lawsuits, the government in the 1990s offered apologies and financial compensation to some of the human radiation testing victims.

Important Points:

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

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

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## Principal

**Respect for Persons**

Individuals should be treated as autonomous agents

Persons with diminished autonomy are entitled to protection.

**Beneficence**

Human participants should not be harmed

Research should maximize possible benefits and minimize possible risks

**Justice**

The benefits and risks of research must be distributed fairly

## Application

**Informed Consent**

Participants, to the degree that they are capable, must be given the opportunity to choose what shall or shall not happen to them

The consent process must include three elements:

- Information
- Comprehension
- Voluntary participation

**Assessment of risks and benefits**

The nature and scope of risks and benefits must be assessed in a systematic manner

**Selection of participants**

There must be fair procedures and outcomes in the selection of research participants

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

**Related Link:** hhs.gov/ohrp/humansubjects/guidance/belmont.htm



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**Sources:**

US Department of Health and Human Services, Office for Human Research Protections

Claremont Graduate University Office of Research, Sponsored Programs, and Grants