Chapter Overview

The protection of human subjects in research is paramount to any research effort. Research that involves human subjects is highly regulated by federal, state, and institutional policies and requirements. Protection is extended to almost every type of research that involves people, even survey research. The purpose of this chapter is to explain the federal regulations that govern research involving humans, to clarify the authority of the institutional review board (IRB), and to address the responsibilities of investigators conducting research using human subjects.

Regulatory Protection of Human Subjects in Research

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Learning Objectives

• Describe, discuss, and define the history of protection of human subjects.
• Describe and discuss the need for protection of human subjects.
• Outline and discuss the Belmont Principles.
• Describe the functions of the institutional review board.
• List the elements of informed consent.

Introduction

It is common for health professionals to perform projects or other activities that involve data collection, analysis, and interpretation. The use of data for the purpose of drawing conclusions and solving problems is usually defined as research; however, many activities considered to be research (e.g., quality improvement, program evaluation, etc.) may not qualify as “regulated research” that requires the approval of an institutional review board (IRB). Although these activities share many of the data collection and analysis methods used by researchers, the outcomes serve different purposes. For example, nonregulated research activities
(i.e., quality improvement, program evaluation, or community outreach) produce results to be used internally or locally to influence immediate change. In contrast, regulated research (i.e., clinical trials) results are widely applicable and generally not used to influence immediate change to the local organization or community. Health professionals may find it difficult to determine whether a particular activity is regulated research and whether it requires the approval of the IRB. After reading this chapter, the reader should have a basic understanding of human (regulated) research, how such research is regulated, and what responsibilities the researcher has when conducting a regulated research project.

**HOW IS RESEARCH APPROVED?**

Before involving living individuals in regulated research, the project and the protections provided by the investigator must be reviewed by the institution’s committee designated to oversee such research. This committee is commonly referred to as the institutional review board (IRB). The IRB is composed of scientists, nonscientists, and individuals who are not affiliated with the institution (sometimes referred to as community members). Members of the IRB are selected based on their expertise in the types of research typically reviewed by the board or on the diversity of their background or experience. The goal of the IRB review is to ensure the individuals participating in the research are adequately protected. To achieve this goal, the IRB reviews the written plan for conducting the research and the safeguards that will be provided to protect participants. The IRB must conclude that the research fulfills the basic principles for conducting ethical research established by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research.²

In 1979, the National Commission released the Belmont Report, which established three basic ethical principles for conducting research involving humans.² (See Table 2–1.) The Belmont principles are respect for persons (autonomy), beneficence, and justice. Application of the general principles led to the development of the following requirements:

**Table 2–1  Belmont Principles**

<table>
<thead>
<tr>
<th><strong>Respect for Persons</strong></th>
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<td>• Treat individuals as autonomous agents capable of making informed choices and acting on them.</td>
<td></td>
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<tr>
<td>• Individuals with diminished autonomy are entitled to protection.</td>
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**Beneficence**

• Maximize possible benefits and minimize possible harms

**Justice**

• Fairness in distribution of the benefits and burdens

Informed consent, assessment of risks and benefits, and equitable selection of subjects. The National Commission was established by Congress in the National Research Act of 1974. The act requires researchers funded by the U.S. Department of Health, Education, and Welfare (now the U.S. Department of Health and Human Services [HHS]) to obtain IRB approval and informed consent. This regulation, 45 CFR Part 46, Subpart A,³ became known as the Common Rule when it was adopted by 15 federal agencies in 1991.⁴ In addition to the Common Rule, the Food and Drug Administration’s (FDA) regulations⁵,⁶ for the protection of human subjects (21 CFR Parts 50 and 56) require IRB approval and informed consent for research involving drugs, devices, or biologics, regardless of the funding source. Finally, the Privacy Rule (45 CFR Part 164)⁷ requires additional approval by a privacy board when research involves identifiable health information held by health-related entities, regardless of the funding source or whether the research uses a drug, device, or biologic. See Figure 2–1.

**WHEN IS IRB APPROVAL REQUIRED?**

IRB approval is needed whenever a project meets the regulatory definitions of human-subjects research provided in either the Common Rule³
The Common Rule is generally applicable to most research conducted by healthcare professionals. Although the Common Rule is technically only applicable to federally funded or supported research, most institutions apply it to all research, regardless of the funding source. The Common Rule requires IRB approval of all “human-subjects research.” Two questions help identify activities as human-subjects research: Is this regulated research? and Are human subjects involved?

**Is This Regulated Research?**

The Belmont Report noted that the distinction between research and practice (non-research) is blurred. The Common Rule defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

Unfortunately, the two key concepts in the definition—“systematic investigation” and “generalizable knowledge”—are not clear. The definition is not particularly helpful in defining regulated research because many other activities such as patient satisfaction surveys and ward infection surveillance would be considered systematic investigations. Jeff Cooper (personal communication, May 2010) notes that a major problem with the definition of “[regulated] research” is the question, “What constitutes generalizable knowledge?” He suggests that “generalizable” should be interpreted as a matter of policy to mean “widely applicable.” This interpretation has the advantage of meeting the common intuitive interpretation of “[regulated] research” and maximally carving out scholarly activities.
In general, the purpose of research is to fill a gap in the current knowledge. The Belmont Report describes research as “...an activity designed to test a hypothesis, permit conclusions to be drawn.” If the conclusions drawn from the activity are widely applicable, one could say the results are generalizable. Research activities that meet both parts of the definition (systematic and generalizable) are considered to be regulated research.

**Are Human Subjects Involved?**

When it has been determined that an activity meets the regulatory definition of research, the next step is to decide whether the research involves human subjects. Regulated research involves human subjects if the researcher either obtains data through interacting or intervening with a living individual or obtains private identifiable information about a living individual. Interacting means the researcher communicates or has interpersonal contact with the individual (e.g., makes phone contact for recruitment or obtains consent to participate). Intervening includes physical procedures (e.g., obtaining blood), manipulating the individual (e.g., providing a treatment), or manipulating the individual’s environment (e.g., changing room temperature). Information is considered private when it is provided for a specific purpose by an individual and the individual can expect it will not be made public. Private information is considered individually identifiable if the identity of the individual may be ascertained by the investigator or associated with the information. Whether or not an activity meets these criteria, it is still necessary when considering whether it is research under the FDA human protections regulations.

**Is This FDA-Regulated Research?**

Although it is uncommon for students and practicing professionals in healthcare professions to conduct research that is FDA regulated, FDA regulations should be considered to determine if IRB approval and informed consent are required. The FDA often uses the term clinical investigation to indicate research. FDA-regulated research includes the following:

- Use of an unapproved drug or biologic
- Use of an FDA-approved drug other than the use of a marketed drug in the course of medical practice
- Use of a device to evaluate safety or effectiveness of that device
- Submission of data from the use of a drug or device to the FDA for advertising or a change in labeling.

If a study involves any of these, the IRB should be contacted for guidance. Not only will IRB approval and informed consent be required, but additional FDA permissions may be necessary before the research can begin. If the activity meets either the Common Rule or FDA definition of human subject research, it will generally be reviewed by the IRB unless it qualifies for an exemption to the Common Rule.

**Can It Be Exempted?**

If a regulated human-subjects research project is not subject to the FDA human protection regulations (as described previously) and does not involve incarcerated individuals (i.e., prisoners), it may qualify for exemption from the Common Rule. Certain regulated human research studies that involve very little or no risk and fall completely within one or more specific exemption categories (as defined in the regulations) may qualify for exempt status. This means that the institution is not required to follow the Common Rule with respect to the research (e.g., obtain IRB approval). However, other rules may be applicable to an exempt study. In general, the institution or a higher authority establishes policy for approving/overseeing exempt human research. For example, because IRB approval is not required, most institutions designate an office or official to make a determination that the research is exempt. Currently, the Office for Human Research Protections (OHRP, a subdivision of HHS) does not recommend that investigators be given the authority...
to make an independent judgment. Most local policies applicable to exempt research are based on the Belmont Principles. (IRBs should be consulted for specific guidance.)

Examples of the most common types of research that can be exempted include (1) educational research involving normal educational practices such as comparing different curricula or instructional techniques, (2) surveys (not involving children) that collect information that would not likely pose a risk to those completing the survey if their answers were released (either because the information is not sensitive in nature or because it cannot be traced back to the individual), or (3) chart reviews of health information that is both preexisting and not traceable back to the individual. An institution’s IRB generally provides the complete list of exemptions from the Common Rule.

If a research project does not meet the criteria for exemption (nonexempt regulated human-subjects research), it must be reviewed by the IRB. In reviewing nonexempt regulated research, the IRB can use one of two review processes: (1) expedited review or (2) review by a meeting of the IRB.

**Can It Be Expedited?**

Some nonexempt studies that involve only minimal risk to participants and fall completely within one or more specific expedited categories may be eligible for an expedited review procedure. The IRB chairperson or one or more experienced members of the IRB may carry out an expedited review instead of the study being reviewed by the convened board. It is necessary to understand the concept of risk when determining if a study is eligible for expedited review. Risk is a measure of harm. It refers to both the likelihood (i.e., probability) that harm may occur and the magnitude of possible harm. Although investigators often focus on physical harms when developing their IRB application, the IRB views harm more broadly. Harm can be categorized as physical (e.g., injury or pain), psychological (e.g., anxiety or shame), social (e.g., adverse effect on relationships), economic (e.g., financial costs), legal (e.g., arrest or lawsuits), or dignitary (e.g., violates personal values).

Like the regulatory definition of human-subjects research discussed earlier, the meaning of minimal risk is a source for debate and may be defined differently by different IRBs. In general, minimal risk means the risks from research activities are not greater than those ordinarily encountered in daily life. Recognizing the debate over whether daily life should be taken to refer to an absolute (i.e., daily life of healthy individuals) or relative (i.e., daily life of participants of the research), many IRBs consider any activities outside those conducted during a routine physical or psychological examination as carrying more than minimal risk. Examples of minimal-risk procedures that meet this definition include simple venipuncture, physical examinations, magnetic resonance imaging (MRI) procedures (not involving contrast), surveys or interviews, and the like. If the risk is no more than minimal, the next step in determining whether the study is eligible for expedited review can be undertaken. The list of planned research activities is then compared with the expedited review categories.

The categories of research eligible for expedited review include the following: research on approved devices that will be used in their approved manner; the study of approved drugs in a manner that does not increase the risk or decrease the acceptability of the risk associated with the use; collection of blood in limited quantities over specific time periods; noninvasive collection of biological specimens (e.g., urine, leftover specimens collected for other purposes); noninvasive data collected routinely in clinical practice that do not involve x-rays, general anesthesia, or sedation (e.g., MRI, weight, blood pressure); use of information or specimens that have already been collected for any purpose; use of information or specimens that will be collected solely for non-research purposes (e.g., medical record reviews); recordings (e.g., voice recordings, digital images); and surveys, focus groups, or interviews.

It is important to remember that the study cannot include any procedures that are more than...
minimal risk and that all research procedures must fall into one or more of the expedited categories. An example of a research study that may involve minimal risk but does not fall completely within the expedited review categories is a study involving the use of health information normally collected as part of routine dental care and a dental x-ray being completed for research purposes. The risk of all the research procedures may be categorized as no more than minimal risk. However, the dental x-ray procedure does not fit any of the expedited review categories (i.e., noninvasive data collection is not appropriate because this procedure involves x-rays). Therefore, although the risk to the participants may be minimal, the research study is not eligible for expedited review (at least initially) and would be reviewed by the convened IRB. If the convened IRB determines the study involves no more than minimal risk, future IRB reviews of the study may be completed using the expedited review procedure.

**How Will the IRB Review a Regulated Research Project?**

For the IRB to approve research, it must determine the following:

- **The risks to the participants have been minimized.** In other words, the probability and magnitude of the reasonably expected research harms have been minimized. However, the nature of the study may limit the extent to which risks can be minimized. Some ways researchers can minimize risks are by choosing a procedure that would pose less risk to the participants over another or designing the study to use procedures that would be performed regardless of whether the individual was enrolled in the research.

- **The risks are reasonable in relation to anticipated benefits.** Once the risks have been minimized, the possible benefits associated with the research are considered. In general, research can potentially benefit individual participants (direct benefit) and/or society (important knowledge gained). An assessment of risks to potential benefits is often referred to as a risk–benefit ratio. The IRB will approve only research where the probability of a benefit outweighs the risks of participating in the research.

- **The selection of subjects is equitable.** With a clear understanding of the risks and potential benefits in the study, consider whether the selected population fairly distributes the burdens and benefits of the research. In making this determination, the IRB considers whether the study targets individuals who will likely benefit from the outcome of the research. For example, the board may ask whether there are participants who may benefit more from the study.

- **Informed consent will be sought from each prospective subject or the subject’s legally authorized representative.** Because informed consent is one of the three basic protections provided by the Common Rule, the IRB will require it in most cases. The human-protection regulations define the basic information that must be provided while obtaining informed consent (see Table 2–2). In some cases, a request may be made that some or all of the elements of consent be waived by the IRB. For example, a waiver of all elements of consent may be appropriate.
for a study using existing health information that was collected for clinical purposes where it is not feasible to obtain consent from the individual patients. An example of an alteration of informed consent (omitting some elements) would include a study where some of the required information is not appropriate for the research. In this case, the investigator can request an alteration in consent if the study meets the criteria for alteration of consent. In addition to the information provided during the consent process, the IRB also evaluates the researchers’ plan for obtaining informed consent. A recruitment plan should provide ample opportunity for prospective participants (or their legally authorized representative) to make an informed choice. Considerations include the study setting, how and by whom the consent interview will be conducted, and timing for obtaining consent (to minimize the possibility that prospective participants may perceive undue pressure to enroll or feel coerced). The informed consent will be appropriately documented. The investigator must have clear plans for obtaining appropriate signatures of participants (or their legally authorized representative) to document the informed consent process. Most IRBs provide a consent document template that provides the basic elements of consent. If this documentation is not possible (e.g., telephone surveys), the investigator may request a waiver of documentation of informed consent, which must be approved by the IRB. In these situations, the researcher must make a note in the research record that all of the required information (see Table 2–2) about the study was presented to the participant and the participant willingly agreed (consented) to participate in the research. The research plan makes adequate provision for monitoring the data collected to ensure safety (when appropriate). When required, a plan for monitoring the safety of the study using the data collected should be developed. This plan should include (1) how often safety data are compiled and reviewed, (2) by whom (an individual or committee), and (3) whether limits are needed for stopping the research procedures to ensure safety of the participants. A formal

![Diagram of Criteria for IRB Approval](image-url)
There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data (when appropriate). For example, assigning study codes to participants rather than using names and storing the key to decipher the codes in a separate, secure location accessible only to the investigators is a way of demonstrating this type of protection.

In addition to the seven determinations just listed, if a study involves populations vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, or mentally disabled (decisionally impaired) people, the IRB will

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**Table 2–2 Elements of Informed Consent**

Basic elements of informed consent provide participants with the following information:

**A statement that the study involves research**
- An explanation of the purposes of the research
- The expected duration of the participant’s participation
- A description of the procedures to be followed
- Identification of any procedures that are experimental

**Description of any reasonably foreseeable risks or discomforts**

**Benefits that may reasonably be expected**
- To the participants (if applicable)
- To others

**Alternative procedures or treatment, if any, that might be advantageous to the participant**

**Confidentiality of records**
- The extent, if any, to which confidentiality will be maintained

**Injury-related care or compensation** (for research involving more than minimal risk)
- Whether any compensation and medical treatments are available if injury occurs
- If so, what they consist of, or where further information may be obtained

**Contact information: whom to contact**
- For answers to pertinent questions about the research and participants’ rights
- In the event of a research-related injury to the participant

**Participation remains voluntary**—no penalty or loss of entitled benefits
- By refusing to participate
- By discontinuing participation at any time

**Additional information when determined to be appropriate by the IRB**
- A statement that the particular treatment or procedure may involve unforeseeable risks
- Anticipated circumstances under which the participant’s participation may be terminated by the investigator without regard to the participant’s consent
- Any additional costs to the participant that may result from participation in the research
- The consequences of a participant’s decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the participant’s willingness to continue participation will be provided to the subject
- The approximate number of participants involved in the study
evaluate whether the study provides safeguards capable of protecting the rights and welfare of those individuals.

In preparing a research project for review by the IRB, the study plan should be designed with the required IRB determinations in mind. Although it is the IRB’s responsibility to determine whether these requirements for approval are met, it is the investigator’s responsibility to design and carry out the study plan in such a way that the criteria for approval are met. This is one of several responsibilities assumed by the investigator responsible for the research.

**WHAT ARE THE INVESTIGATOR’S RESPONSIBILITIES?**

Obtaining IRB approval for a new project is only the first of many responsibilities for the principal investigator (PI). During the conduct of the study, the PI must ensure the study continues to meet the criteria used by the IRB for the initial approval (e.g., the risks continue to be minimized, informed consent continues to be obtained and documented, safety data are collected and monitored, etc.). The PI is also responsible for communicating regularly with the IRB under certain circumstances such as those described in the following sections.

**Continuing Review**

Many investigators do not realize that the approval they get when a study is first reviewed by the IRB has a time limit that cannot exceed 1 year. To request reapproval so that the research can continue uninterrupted, the PI must submit a status report to the IRB before the approval period expires. The report must include information about the number of participants accrued (if any); a description of any adverse events, unanticipated problems, participant withdrawals, or complaints; a summary of relevant new information (either published or learned in the research); and a copy of the current consent document(s) being used. The IRB reviews the status report, including any other new information, and reconsiders the required determinations for approval of research (e.g., risks continue to be minimized, risks continue to be reasonable in relation to the benefits, informed consent continues to be obtained and appropriately documented, etc.). If the study continues to meet the criteria for approval, the IRB will reapprove the study for up to one additional year.

Sometimes the IRB may decide to issue an approval for less than a year (e.g., for particularly high risk studies the IRB may approve the study for only a few months). It is the responsibility of the investigator to contact the IRB to request reapproval prior to the expiration of the original IRB approval. If the IRB has not reapproved the study before the current approval period expires, research procedures (including analysis of identifiable data) may not be performed.

**Modifications**

When changes to a research study are needed, IRB approval must first be obtained before the modification is implemented. Changes may be made to a study without prior IRB approval only when the modification is necessary to eliminate an immediate hazard to the participants. Examples of changes that must be approved by the IRB are changes in the number of participants needed to enroll; changes to the study design, methods, or procedures; changes to study sites or locations; changes in consent procedures and/or consent document; changes in recruitment materials; and changes in compensation amounts. Each IRB establishes a mechanism for requesting approval of modifications. Like new studies, the IRB may use expedited or full-committee review procedures. Minor changes to already approved studies are generally eligible for expedited review.

**Tracking Adverse Events and Reporting UPIRSOs**

Adverse events can be expected in research. A good data safety monitoring plan allows investigators to track adverse events that occur during a research
study and to continuously monitor them to determine whether changes should be made to the research plan to minimize risks to participants.\textsuperscript{14} Although adverse events should be tracked, not all occurrences must be reported to the IRB immediately.

Only adverse events that meet the criteria of an UPIRSO (Unanticipated Problem Involving Risks to Subjects or Others) must be reported immediately to the IRB. A UPIRSO is any incident, experience, or outcome that meets \textit{all} of the following criteria\textsuperscript{14}:

1. Unexpected (in terms of nature, severity, or frequency), \textit{and}
2. Related or possibly related to participation in the research, \textit{and}
3. Suggests that the research places participants (or others) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Although some UPIRSOs are also adverse events, keep in mind that not all UPIRSOs are adverse events. UPIRSOs may result from other problems such as the unintentional loss of identifiable private information that represents increased likelihood of harm, rather than actual harm. The IRB will review the UPIRSO and determine whether the research should continue and whether modifications should be made to the research to offer additional protection to the participants or others.

**Reporting Noncompliance**

Instances of noncompliance should be reported by the PI to the IRB. Noncompliance is an action by the investigator or member of the research team that disregards or violates federal regulations, IRB requirements and determinations, or institutional policies and procedures.\textsuperscript{12} When noncompliance is discovered, the IRB reviews the events surrounding the incident; the seriousness of the event and whether it has occurred before; and the event’s effect on the participants’ rights, welfare, and safety. The IRB often requires a written report from the investigator that includes a corrective action plan. The IRB may decide that additional actions are necessary to address the noncompliance; such actions may range from retraining the PI or study staff to suspension or termination of the research (depending upon the severity of the event). If the IRB determines the noncompliance is either serious or continuing, the event is reported to the OHRP (for research funded by HHS) and/or the FDA (for certain FDA-regulated research).\textsuperscript{3}

**Inactivation**

The investigator should notify the IRB when the study has concluded or when the IRB approval is no longer necessary. An IRB approval may be inactivated if \textit{all} of the following are true:

- Enrollment is permanently closed to new participants.
- Data, private information, and/or specimens are no longer being collected for research purposes (including long-term follow-up).
- Participants are no longer being treated under the research protocol and there are no plans for future research treatment.
- Research assessments or procedures are no longer being performed and there are no plans for future research procedures.
- Data or specimen analysis has been completed, or if analysis continues, the materials undergoing analysis will be deidentified.
- Federal research funding for the study is closed (if applicable).
- The study is closed at all participating sites that are under the investigator’s supervision.

The investigator notifies the IRB of the intent to inactivate the IRB approval by providing a final status report to the IRB. The IRB reviews the status of the study and determines whether inactivating the approval is appropriate.

**Additional Responsibilities**

In addition to the responsibilities of the investigator to the IRB as outlined in the previous sections, the following additional responsibilities are expected of PIs\textsuperscript{15,16}:
• Complete and maintain training on human-subjects protection. Each institution has its own training requirements. (Several courses are available on the Internet. As a public service, the NIH Office of Extramural Research offers a free tutorial on “Protecting Human Research Participants” that institutions may elect to use to meet the human-subjects protection education requirement.)
• Follow the IRB-approved protocol and the regulations and policies related to research and privacy.
• Supervise everyone working on the project to ensure they follow the protocol and rules that govern research.
• Place the protection of research participants first.
• Verify IRB approval before allowing research to begin or before implementing changes.
• Keep participants informed and ensure they are willing to continue participating. Informed consent occurs at the beginning of research participation and should continue throughout a participant’s involvement in the research.
• Regularly collect and assess information about safety or unexpected problems. This includes conducting regular literature reviews for new information that may affect the study or the study participants.
• Ensure those working on the project are qualified and are authorized to perform delegated tasks. This includes education, training, experience, and certifications.
• Provide ongoing communication with study staff. This communication allows the PI to assess problems as they arise and to make swift changes as necessary.
• Confirm that the data collected are accurate.
• Maintain organized records.

By following these guidelines, the PI protects research participants and improves the quality of the research conducted.

SUMMARY

In conclusion, a number of complex federal regulations govern research involving human subjects. This chapter provided a brief introduction to the major concepts involved in complying with the regulations. Understanding these concepts is essential for health professionals who must understand the basic ethical principles that guide research and their responsibilities to comply with the rules and regulations applicable to the type of research they may conduct. Investigators and their IRBs must work together to ensure that research is conducted safely and in an ethical manner. When any regulated human-subjects research project is planned, the local IRB should be contacted for assistance.

REFERENCES


